ANNALS of ALLERGY

Published by the
American College of Allergists

Volume 4 November-December, 1946 Number 6

DIFFERENTIAL DIAGNOSIS OF BRONCHIAL ASTHMA IN INFANCY AND CHILDHOOD

JEROME GLASER, M.D., F.A.C.A.
Rochester, New York

THE differential diagnosis of bronchial asthma at any age is not commonly attended with any great difficulty. That this is true is attested chiefly by two facts: (1) the brevity and incompleteness of the definitions given in textbooks for the term, "bronchial asthma," and (2) the little space usually allocated to any discussion of the subject of differential diagnosis, particularly in pediatric literature. There are a number of excellent presentations of the problem of the differential diagnosis of bronchial asthma in adults, among the more recent of which may be mentioned that of Sodeman.[36]

In the most recent textbook on asthma, that of Unger[39], bronchial asthma is defined as follows: "Bronchial asthma, a common condition occurring at any age, is caused by incomplete bronchial obstruction, usually induced by hypersensitivity to one or more allergens, and characterized by attacks of dyspnea and wheezing." This definition depends for its accuracy upon the proof that the wheezing is usually caused by identifiable allergens. However, in the most troublesome form of asthma, the so-called "intrinsic asthma," the causative allergens cannot be demonstrated. Dyspnea and wheezing alone are not sufficient to make a diagnosis because these accompany a multitude of conditions besides bronchial asthma.

A suggested definition for bronchial asthma is as follows: bronchial asthma may be defined as a form of obstructive emphysema of allergic origin, involving both lungs throughout, characterized by paroxysmal attacks of dyspnea, chiefly expiratory, accompanied by wheezing heard on auscultation of the chest and typically relieved, at least in the early stages

From the Department of Pediatrics of the University of Rochester School of Medicine and Dentistry and the Pediatric Services of the Strong Memorial, Rochester Municipal and Genessee Hospitals, Rochester, N. Y.
Presented in part as a clinical lecture at the Graduate Instructional Course of the American College of Allergists, Thorne Hall, Northwestern University, Chicago, Ill., November 8, 1945.

of an attack, by sympathomimetic drugs. The pathological physiology consists of edema, increased secretion of the mucous glands, spasm of smooth muscle, and usually a local tissue and fluid eosinophilia.

The above definition emphasizes the important fact that bronchial asthma is only one form of obstructive emphysema. It is, however, the most common form. If this fact is kept in mind the use of the confusing term, "non-allergic asthma," may be avoided. All so-called non-allergic asthmas are other forms of obstructive emphysema and should be so designated. That true bronchial asthma is of allergic origin is beyond dispute in the present state of our knowledge although unfortunately it is not always, and some would say not commonly, possible to demonstrate the etiological allergens. Dyspnea, chiefly expiratory, is an intrinsic part of the clinical picture of bronchial asthma although it is also common to other forms of obstructive emphysema. True bronchial asthma involves both lungs throughout and not merely parts of the lungs. The wheezing must be heard on auscultation of the chest. In some forms of obstructive emphysema there is no wheezing audible at the chest wall although wheezing can be demonstrated on auscultation at the nares or mouth.

It is important to remember that at one stage of its development bronchial asthma is always completely and satisfactorily relieved by the administration of a sympathomimetic drug (ephedrine, epinephrine hydrochloride, et cetera). This relief must be complete and unequivocal. The statement so often made in the physician's or nurse's notes to the effect that such a drug was given during an attack and "the patient appeared to be slightly improved" means nothing with regard to the diagnosis. So far as I know Ratner[32] was the first to emphasize relief by an appropriate drug as part of the definition of bronchial asthma. It should be further emphasized that the diagnosis of bronchial asthma is a clinical and not a laboratory diagnosis. The patient should not be referred to the allergist for skin testing "to see if he has bronchial asthma." While in most instances the diagnosis may be made with accuracy from the history alone, yet it cannot be absolutely established unless the patient is examined during an attack.

There is no hard and fast line of demarcation between allergy in pediatrics and allergy in internal medicine. The pediatric allergist must be thoroughly familiar with infant feeding, environmental control, the special peculiarities of the skin of infants, and the special techniques employed in the testing of infants and young children. It is particularly important for the pediatrician to know well the little that is known regarding the prophylaxis of allergic disease.[14,21] The internist who is also an allergist must particularly consider allergy in its relationship to the degenerative and neoplastic diseases of adult life. In the discussion of the differential diagnosis of bronchial asthma, it is particularly interesting that there is practically no condition simulating bronchial asthma in an adult which

may not also simulate the same condition in a child. The opposite (with the possible exception of "thymic asthma") is also true.

Bronchial asthma may appear at any age; apparently it may appear to start at birth. The literature on this subject has been reviewed by Bray.[5] Generally speaking, however, the older the age group, the more bronchial asthma will be found. In my practice, which is largely pediatric allergy, I see each year an average of four to six infants under one year of age with attacks of bronchial asthma (as distinguished from those seen with a history of attacks starting under one year of age). However, asthma does not begin to be a significant problem until about the age of four or five years. The classical sequence is as follows: colic (starting most commonly at about the age of three weeks); atopic dermatitis (infantile eczema) starting a few weeks later; recurrent upper respiratory infections starting between two and three years of age; then the development of pollinosis or perennial allergic rhinitis; then bronchial asthma. This progression is typical but not invariable. Any or all of the commonly preceding conditions may not appear, and bronchial asthma may develop its complete clinical picture at any age.

There are certain important differences in the symptomatology of bronchial asthma between children and adults. This is particularly true of children two years of age or less. This is probably correlated with the fact[23] that the infantile type of respiration, chiefly abdominal, changes toward the adult type, chiefly thoracic, beginning with the assumption of the upright position. This as a rule is well under way by the end of the second year.

The chief differences are as follows:

The dyspnea is not necessarily expiratory in character. It may resemble an ordinary dyspnea.[20] It is, however, very difficult to time the respirations accurately in a dyspneic infant, and the picture is further confused by the fact that the chest is small and round, and sounds are easily transmitted from distant parts. I have the impression that even at this age expiratory dyspnea is more marked than inspiratory, and if this is not true then the diagnosis must be more carefully questioned than otherwise.

It is striking that the asthmatic infant may be perfectly comfortable even when flat on his back.* This is in significant contrast to the older child or adult where the absence of orthopnea may cause doubt as to the diagnosis. This is doubtless due to the type of breathing normal at this age and the greater softness and flexibility of the thoracic cage.

The absence of anxiety on the part of the infantile patient in a severe attack of asthma is in striking contrast to that of the adult. An infant may be wheezing loudly and apparently have great difficulty in breathing, and yet his attention may be distracted and he may even be made to smile by dangling a rattle or other toy in front of his eyes. The parents are

*This was first directed to my attention early in my work in pediatric allergy by Dr. Stearns S. Bullen.

commonly much more anxious than the child. I can recall only one infant who had the expression of fear of impending death in her eyes. This was a child whose attacks had started at the age of three months. At six months she had a very severe attack and failed to respond to injections of epinephrine hydrochloride. This was thirteen years ago when aminophyllin and helium and oxygen were not yet used in the symptomatic treatment of asthma. The infant was relieved by a small dose of morphine. Such treatment would now be considered almost heresy, yet there are even now occasions when all other measures fail when a small dose of an opiate (one half to one quarter of the usual dose) may turn the tide in favor of the patient. The dose for an infant may be computed by the weight-dose method in the same manner as computing the dose for older children. This was demonstrated by Irich.[18] I now try demerol first and believe this is more effective with infants and children than with adults.[15] The next choice is dilaudid. Barach[4] is one of the few leaders in the field of symptomatic treatment of bronchial asthma who concurs in the use of small doses of opiates, preferably dilaudid, under suitable indications.

The problem of fever in relationship to attacks of asthma in infancy and early childhood has not yet been completely worked out. In my own experience uncomplicated bronchial asthma in this age group may be accompanied by a very slight increase in the rectal temperature (over 37.7° C. or 100° F.). This rise does not commonly amount to more than 1.5° F. (0.8 C.) It is probably due to the increased metabolism of muscle effort accompanying the dyspnea.

One of the most interesting physical signs in bronchial asthma, or any other form of bilateral obstructive emphysema, is the early disappearance of the normal area of cardiac dullness. This sign must be elicited with care as the area is normally very small at this age. A corollary to this is the increase in size of the clear areas in front of and behind the heart on fluoroscopy or roentgenograms in the lateral and oblique positions.

When the diagnosis of bronchial asthma is questionable, a favorable response to epinephrine hydrochloride or other sympathomimetic drug is specific, as has been discussed previously. The question of the dose of epinephrine hydrochloride is important. Unfortunately there is no practical weight dose formula for this drug at any age since the individual response is so variable. The proper dose at any age is that which gives the maximum therapeutic response with a minimum of disagreeable side reactions. It must be remembered that infants are more readily shocked by epinephrine hydrochloride than older individuals and that great care must be used in administering this drug in infancy. Under one year of age one should start with 0.10 c.c.; if no relief is obtained 0.15 c.c. may be given in fifteen to twenty minutes; if there is still no relief then the dosage may be increased by increments of 0.05 c.c. every fifteen minutes until relief is obtained or until it is evident by the usual signs (pallor,

cold sweat, tremor, patchy cyanosis, anxiety, nausea, vomiting) that the patient is getting the disagreeable side reactions of epinephrine hydrochloride without relief and therefore is "fast" to the drug. In infancy and early childhood the amount required to obtain adequate relief is not commonly more than 0.20 to 0.35 c.c., though rarely a higher dose is necessary and is well tolerated. Should the infant respond favorably to a given dose, a note should be made as to the amount so that this may be used as a starting dose in subsequent attacks of equivalent severity. Because of the speed of action of this drug, before injection the plunger of the syringe should be pulled back a little to make sure that the opening of the needle is not in the blood stream.

Favorable complete and unequivocal response to aminophyllin, at least in infants and children where a possible cardiac factor as a cause of the dyspnea need not commonly be considered, is probably also specific for the diagnosis of bronchial asthma. However, this cannot be stated with certainty until more information is at hand regarding the effect of aminophyllin in forms of obstructive emphysema other than bronchial asthma.

If a child is seen between attacks, latent wheezing may occasionally be demonstrated by having the child expire forcibly. This procedure was described by Clarke.[9] If the child is old enough, co-operation may be obtained by asking him to "Blow hard, just like you blow out the candle on a birthday cake," or some similar request. If the child will not cooperate the same effect may be produced by having him become breathless from exercise, or, in the case of an infant, by making him cry. The value of this sign is illustrated by the following case report:

Case No. 6109. This boy was first seen at the age of seven months because of wheezing which had been observed since he was a month old. Because this was not at all troublesome he was not brought to a pediatrician until he was three months old, when the mother wished advice regarding feeding. At this time asthma was suspected and the diagnosis appeared to be confirmed when the wheezing stopped after the administration of a test dose of epinephrine hydrochloride. When seen by me four months later the child was still wheezing but the attacks continued to be very mild. There was no history of asthma in the immediate family although there was bronchial asthma on the maternal side. Physical examination was normal except for faint, high pitched wheezing sounds on inspiration throughout both lungs. Fluoroscopy and roentgenograms in various positions revealed normal findings. On taking a post-nasal smear for eosinophils the child cried vigorously, the wheezing disappeared and no râles could be heard on ascultation of the chest. The mother then stated in response to questioning that the child had cried when given the test dose of epinephrine hydrochloride some months previously. I believe tnat the facts that the dyspnea was inspiratory and disappeared on crying effectively rule out bronchial asthma in this case and that the child has a congenital stridor, the origin of which remains to be determined.

The demonstration of eosinophils in the mucous secretion of the respiratory tract is an important diagnostic procedure, because if these are found in significant numbers, the burden of proof rests with the physician

who states that the child does not have allergic disease. My experience with direct smears of mucus from the nose or pharynx of young children was not uniformly successful, especially when the secretion was scanty, until it was discovered that continuous direct contact of the swab with the mucous membrane for at least one minute would almost always result in positive smears in the case of an allergic mucous membrane. Infants and young children will not tolerate for even a minute the presence of tightly wound cotton, even when not attached to a wire or toothpick, in their nasal passages without crying. The tears passing through the nasolachrymal duct into the nasal cavity wash the swabs free of cells. However, on adapting the Bradford[3] post-nasal flexible wire swab for this test, it is relatively simple to obtain good smears. These swabs, which consist merely of a cotton tip thinly, tightly and evenly wound around a strand of flexible copper wire, were originally devised by Bradford for taking post-nasal cultures for detecting the presence of pertussis bacilli. When adapted for the purpose of demonstrating eosinophils, the child is held firmly on his back, the swab inserted until its tip rests against the posterior pharyngeal wall, and the child then turned over onto his abdomen for a minute so that the tears will not flow back against the swab. The swab is then removed and a smear made which is stained by Hansel's[16] method. A less satisfactory method is to close the openings of the nasolachrymal ducts with the fingertips while the child is forcibly restrained and the nasal swab inserted.

It is not the purpose of this communication to discuss in detail all diseases accompanied by wheezing but only those of most importance or of most interest to the pediatrician because of their possible confusion with bronchial asthma.

ASTHMATIC BRONCHITIS

Asthmatic bronchitis is a term applied to paroxysmal attacks of dyspnea which occur particularly in children but which may occur at any age. Attacks are accompanied by the physical signs of asthma including wheezing and evidence of a respiratory infection. It is an important condition in infancy and childhood because it is relatively common and its relationship to bronchial asthma is uncertain in the minds of many.

Other terms synonymous with asthmatic bronchitis are spastic bronchitis, emphysematous bronchitis, and, especially in very young infants, capillary bronchitis or bronchiolitis. A condition presenting many similarities to asthmatic bronchitis is the "sino-bronchial syndrome, recently described by Dutton and Fuchlow.[12] The main points of difference from bronchial asthma are: asthmatic bronchitis commonly starts with a coryza; fever is usual; there is poor response to sympathomimetic drugs; nasal smears show a preponderance of neutrophils and the sedimentation rate is somewhat increased. However, asthmatic bronchitis, particularly as it occurs in children, has been suspected of being of allergic origin because it is so freqently followed by bronchial asthma as the child grows older.

It is theoretically possible that true asthmatic bronchitis of purely infectious non-allergic origin may occur. As long ago as 1907, Ingals[17], in doing bronchoscopies in children, noted that the bronchial tubes dilate during inspiration and contract during expiration. This observation has been confirmed by many others, including Jackson[19], since then. Under such circumstances it would appear that obstructive emphysema with expiratory wheezing may occur solely as a result of edema secondary to infection or even other causes, as irritating inhalants. The reason that asthmatic bronchitis occurs in children more commonly than in adults may be explained in part by another observation of Ingals that the movements of the bronchi previously mentioned are more marked in children than in adults due to the greater elasticity of the tissues and lesser calcification of the cartilagenous bronchial rings in children as compared with adults.

The question may then well be asked, "If asthmatic bronchitis may be due to a local inflammatory condition, why doesn't wheezing occur in practically all pulmonary infections?" To the author's mind there is a relationship between asthmatic bronchitis and bronchial asthma analogous to the relationship between cardiac asthma and bronchial asthma. Not all persons with cardiac decompensation wheeze. The studies of Swineford and Magruder[37] appear to support the theory first advanced by Rackemann[31] that cardiac asthma is the result of heart failure in an allergic or potentially allergic individual. The fact that asthmatic bronchitis is, in the author's experience, always followed by bronchial asthma, if the child continues to have pulmonary difficulty, would suggest that asthmatic bronchitis is the form which pulmonary inflammation commonly takes in an allergic or potentially allergic child. Just why this happens, of course, remains yet to be explained.

FOREIGN BODY IN A BRONCHUS

Some of the most tragic mistakes in the differential diagnosis of bronchial asthma are made because the physician does not realize that the symptoms and physical signs of asthma may be reproduced to an exceedingly misleading extent by the presence of a foreign body in a bronchus. This is especially true in infancy and childhood because these patients appear at times to exercise almost diabolical ingenuity in getting unsuspected foreign bodies into their bronchial trees. The diagnosis may almost always be made by the roentgenogram, even in the case of a radiotransparent foreign body, because of the local changes produced by its presence. The roentgenogram must be made with care because if too light, for example, a metallic foreign body may occasionally escape detection. *In case of any reasonable doubt concerning the diagnosis, a bronchoscopy is mandatory.* Since the advent of the sulfon compounds and penicillin, the danger of bronchoscopy in competent hands has been greatly reduced. Infants and very young children, for example, may be started

on penicillin eight hours before bronchoscopy and continued for twenty-four hours afterwards or as long as may be indicated by the child's condition.

The following report is typical of simulation of bronchial asthma by a foreign body in a bronchus.

Case No. 5124. This boy was first seen at the age of sixteen months. A month previously while playing on the ground he attracted the attention of his mother by coughing. She noticed that he had some dirt on his face and thought that some might possibly have been swallowed or inhaled. The cough continued and wheezing developed shortly thereafter. The family physician diagnosed bronchial asthma complicated by bronchitis. A consultant said the child had bronchitis but not asthma. The boy would occasionally develop a rectal temperature up to 39.5° C. (103° F.). Throughout the time of my examination, the child cried furiously, and wheezing could not be distinguished. The findings were normal except for increased markings on fluoroscopy in the left hilar region. Because of the possibility that a foreign body might be present a roentgenogram was made. The film showed a pebble in the left main bronchus, and when this was removed, the child's symptoms completely disappeared.

Obstructive emphysema of other types may also simulate asthma. This is well illustrated by the following report.

Case No. 4351. This boy, five and one-half months old, was referred by his physician because of bronchial asthma. The patient's maternal grandmother had asthma and his brother had eczema. The patient himself developed a rash whenever orange juice was ingested. He also had a seborrhoeic dermatitis involving the posterior auricular folds, the external auditory canals and the scalp.

The patient's illness was said to have started with a very severe coryza at the age of three months early in June, and a bad attack of "asthma" occurred late in June. He seemed to suffer more outside of the home than inside. The symptoms cleared considerably when he was taken to a pollen-free resort. However, as soon as he returned to Rochester, which was in early September at the height of the ragweed pollen season, the "asthmatic attacks" recurred almost daily. Ephedrine gave no relief. The attacks had not been considered severe enough to require the injection of epinephrine hydrochloride. The history was consistent with that of bronchial asthma due to the pollen of grass and weeds.

On physical examination the boy was well developed and nourished, and lay comfortably on his back, wheezing loudly. On closer observation it was evident that he had a definite inspiratory stridor with slight retractions of the costal margins. On auscultation no wheezing could be heard over the lungs. On fluoroscopy the lungs presented a remarkable picture which was confirmed by roentgenograms. The heart and trachea and other mediastinal contents were shifted toward the left side. There was a marked degree of emphysema involving the larger part of the right lung with increased transparency. The diaphragm on the right side was depressed and partially fixed with increased excursions of the diaphragm on the left side. The signs were most accentuated at the end of expiration and were typical of unilateral obstructive emphysema as described by Manges.[26]

It was suspected that the etiological factor was a non-opaque foreign body in the right bronchus. The parents refused bronchoscopy. The mother was known to have active tuberculosis but a tuberculin test on the child was negative. He was seen seven months later at the age of one year and appeared to have developed

normally but the chest findings remained the same. He was not seen again until he was two and one-half years of age and that time the chest appeared entirely normal.

CYSTIC FIBROSIS OF THE PANCREAS

Anderson[2] in 1938 emphasized the pulmonary aspects of cystic fibrosis of the pancreas and is chiefly responsible for the numerous clinical studies of this condition which have been made since then. She classified the condition into three main groups: (1) Meconium ileus. In these cases the meconium does not undergo normal pancreatic digestion but persists as a rubbery mass causing death by intestinal obstruction. There is no satisfactory surgical or medical treatment and the patients rarely live longer than a week. (2) A group of cases characterized by failure to gain, even on an adequate diet, in the neonatal period; a large abdomen at birth; hunger; absence of vomiting or diarrhea; intolerance of fat in the diet; and chronic infection of the upper respiratory tract. (3) A group of cases presenting the celiac syndrome[13]: typical wasting, more in the extremities than in the face, and often retardation of growth; distention of the abdomen; and bulky, foul-smelling, frothy stools that contain excess fat. It must be emphasized that cystic fibrosis of the pancreas is only one cause of the celiac syndrome. Among other causes are chronic infections, congenital malformation of the small intestine, dysentery, megacolon, syphilis, tuberculous peritonitis and an idiopathic form.

Dickey[11] in reviewing the subject stated that "in any patient under two years of age with a chronic respiratory infection extending from the tip of the nose to the alveoli, with a negative sputum and a negative tuberculin test, cystic fibrosis of the pancreas should be thought of immediately." The respiratory symptoms are believed to be due to increased vulnerability of the lung to infection because vitamin A is not absorbed, due to failure of absorption of fats which are the usual vehicle of vitamin A. The most common organism found in the lungs is the staphylococcus aureus. There is mild tubular dilatation of the bronchi and bronchioles and squamous metaplasia of the bronchial epithelium. The bronchi are plugged with greenish-gray, mucopurulent material. It is particularly because of these pathological changes that the symptoms of asthmatic bronchitis or asthma are produced. This leads to subjecting children with this disease to allergic study.

The chief laboratory aids in making the diagnosis of cystic fibrosis of the pancreas are: absence of satisfactory response to sympathomimetic drugs as regards the cough and wheezing; absence of eosinophilia in the bronchial secretions; failure to absorb glucose properly as indicated by the glucose tolerance curve; poor absorption of vitamin A as indicated by the vitamin A tolerance test[6,8]; and diminution or absence of pancreatic enzymes on duodenal drainage.

The following case, reported through the courtesy of Dr. Herbert C. Soule, Jr., is a typical example of this disease.

The patient was the third child of normal parents. The family history was interesting in that the child had an older sister with ragweed pollen asthma and a brother who had died on the eleventh day after birth from a meconium ileus secondary to cystic fibrosis of the pancreas. Another sister had developed normally. Starting at the age of three weeks the patient's breathing was observed to be noisy on exertion and asthma was suspected. A roentgenogram of the chest was reported normal. A consulting bronchoscopist suspected a slight stenosis of the larynx. The boy did rather well, however, until about the age of five months when his weight was 7.3 Kg. (16 pounds). Abnormal stools had never been observed. At this time he developed a troublesome cough and considerable dyspnea and asthmatic bronchitis was considered. Epinephrine was injected and appeared to give a little relief. Skin tests done by the consulting allergist were negative. Experimental changes in diet did not help.

At the age of seven months the boy's condition was so serious that he was admitted to the hospital where he died twelve days later. The necropsy revealed subacute bronchitis, bronchiolitis, bronchopneumonia and cystic fibrosis of the pancreas.

THYMIC ASTHMA

Thymic asthma is a condition which was frequently mentioned in medical literature many years ago. It originally referred to a poroxysmal type of dyspnea believed to be due to pressure on the trachea from an enlarged thymus gland. This was first described by Kopp[22] in 1830 and hence is occasionally called "Kopp's asthma." Whether or not this condition actually existed was much debated and greatly doubted. Following the development of aseptic surgery about 1890, when it became possible to remove the thymus surgically, evidence was established by Olivier[28] that Kopp's original contention was occasionally correct. In the great majority of instances, however, the dyspnea eventually proved to be due to some cause other than enlargement of the thymus gland. Because of this and particularly because of the report of the Status Lymphaticus Investigation Committee in England in 1931[42], most authorities felt that this condition did not exist. However, the development of the study of clinical allergy has caused a revival of interest in the study of the thymus as related to dyspnea, the most important contributions being those of Aldrich[1], Waldbott[41], and Carr.[7]

Aldrich stated that in his own experience there were many patients with an expiratory wheeze indistinguishable by physical signs from ordinary bronchial asthma and considered as true bronchial asthma for weeks or months until the true diagnosis of enlarged thymus was made. Aldrich believes that thymic asthma may be related to true bronchial asthma in that both may be considered manifestations of vagotonia. Radiation over the thymus appeared effective in relieving the symptoms whether or not the gland was demonstrably enlarged.

Carr described the pathological findings in what he terms "status thymico-asthmaticus." He states that the clinical course of these cases is distinguished with difficulty from true bronchial asthma except for the single but very important fact that the status thymico-asthmaticus group

shows no beneficial response to the injection of epinephrine. These patients die of asphyxia, and at necropsy more or less enlargement of the thymus is found. He correlated the pathological findings in these patients with those of Waldbott in two cases of death from asthma in infancy. Waldbott was struck by the similarity in findings in these cases to those previously described in so-called thymic death and felt that this condition and death from allergic shock might be equivalent. In Carr's cases the same type of anatomical and cytological abnormalities as that noted by Waldbott was found.

AYERZA'S DISEASE

This is a very rare, chronic pulmonary disease accompanied by wheezing which was first described by Dr. Abel Ayerza of Buenos Aires in 1901. The best description in English is given by Smith.[35] Its etiology is obscure but is probably due to chronic bronchopulmonary changes. In its later stage the disease is characterized by five cardinal signs: (1) dyspnea, (2) polycythemia, (3) chronic cyanosis, said to be the first sign which should make one suspect that the patient does not have bronchial asthma, (4) prominence of the pulmonary cone with right ventricular hypertrophy, and (5) right ventricular preponderance by the electrocardiogram. From one to twenty-five years may be required for the complete development of this syndrome.

Death commonly occurs from cardiac failure. The findings are sufficiently constant to be diagnostic: (1) typical findings of death due to cardiac failure are present; (2) the lungs show the effect of chronic bronchitis and emphysema, and (3) dilatation and sclerosis of the pulmonary arteries are the striking and unusual features.

The following is a brief abstract of the case reported by Smith.

The patient was a thirteen-year-old white girl who was seen because of the following complaints: asthmatic attacks of eight years' duration, cyanosis of six years' duration and headaches of four years' duration. The child's past personal history and her family history were negative for allergy. The condition started at the age of four and one-half years when she began to have attacks of croup and bronchitis, perennial but worse in the winter. She was studied by two competent allergists with completely negative findings and failure to obtain relief. Cyanosis had started insidiously at the age of seven years, and its progress was steady. Headaches were attributed to sinusitis, and in the four years previous to being seen the child had been in Tucson, Arizona, where she showed slight improvement. Studies for tuberculosis were completely negative. Shortly before being seen the child's dyspnea had increased and the cough became very productive, mucopurulent in nature and frequently blood streaked.

On physical examination she was a fairly tall, dyspneic, asthenic girl presenting the typical appearance of a child with long-standing asthma. The most striking feature was a generalized cyanosis. Auscultation of the lungs gave the findings typical of chronic asthma. The heart sounds were normal. There was no clubbing of the fingers or toes. The blood pressure was normal. The blood findings were as follows: red blood cells 6.1; haemoglobin 130 per cent Sahli;

white blood cells 6,200 with 48 per cent polymorphonuclear leukocytes, 42 per cent lymphocytes and 10 per cent eosinophils. The Kahn test was negative. A roentgenogram showed accentuated bronchovesicular markings throughout, an unusually prominent pulmonic cone, widening of the intercostal spaces and depression of the diaphragm.

On bronchoscopy the mucous membranes of the pharynx and tracheobronchial tree were deeply purple, thin and friable. The trachea and both bronchi contained a large amount of exceedingly tenacious material. There was no gross obstruction in the airway. Each branch bronchus was in normal position and its lumen filled with a frothy white secretion. There was no evidence of the anterior-posterior collapse of the bronchi usually seen in a far advanced asthmatic.

The patient died not long after having been studied of an acute respiratory infection, probably pneumonia. Necropsy was not performed.

DUST BRONCHITIS

This type of bronchitis, previously noted in the Dust Bowl area, was described in children by Toomey and Petersilge.[38] It is due to the inhalation of finely pulverized dust, in their cases inhaled by children playing on a large clay field during a spell of warm weather. The principal symptom was an explosive, intractable, non-productive cough, which was exaggerated by excitement, deep breathing or lying on the back. The temperature often reached 38.2°C. (101°F.) but soon became normal after putting the child to bed. Whistling noises were heard in the lungs with loud rhonchi at the bases. Roentgenograms showed only soft, patchy mottling with increased markings along the course of the bronchi. Treatment was symptomatic with sedatives and expectorant cough mixtures.

SIGHING DYSPNEA

As a nosological entity this condition was first described by Maytum and Willius[26] in 1934 and again by Maytum[27] in 1939. It is important to the allergist because, although not accompanied by wheezing, it is often confused with bronchial asthma and referred to the allergist for study. It is a functional disorder of respiration and is not caused by organic disease.

If seen during an attack, diagnosis is easy. There is no wheezing or cough and no evidence of obstruction to respiration. Physical examination is usually normal, but other conditions as asthma and cardiac disease may co-exist and must be properly evaluated. If not seen during an attack the history is characteristic. The patient complains of "shortness of breath," or "inability to take a deep breath," or "I cannot fill my lungs and I get frightened," et cetera. In bad attacks the patient may have a severe dyspnea and appear acutely ill. If the attack is prolonged, tetany may develop. The treatment is psychotherapy.

Prince[29,30] has seen two cases of sighing dyspnea in children but the only report in the literature on children is that of Silberberg[34] who described a case in a boy thirteen years of age. Overwork and strain had made this patient dislike school although he was a bright boy. He be-

came much interested in making a miniature motor car but this was beyond his capacity and caused a sense of frustration. One day in class he found himself gasping for breath, trying to fill his lungs. He continued to take long sighs for about half an hour; then his hands felt paralyzed; he developed parasthesias in his hands, patellae, and about his trunk, and also had a peculiar sensation in his head. These were symptoms of tetany due to hyperventillation. He remained at home for two days. On returning to school a similar attack occurred which alarmed his teacher. The physical examination shortly thereafterwards was negative and Silberberg regarded the boy as manifesting a hyperventillation syndrome. Explanation and reassurance were given and the boy remained well.

THE ASTHMATIC COUGH

No discussion of the problem of the differential diagnosis of bronchial asthma in infancy and childhood would be complete without mention of the symptom of cough. Cough may be regarded as a preasthmatic symptom because it often happens that a persistent cough for which no adequate cause can be discovered eventually develops into bronchial asthma. When such a cough develops in an allergic child the problem of differential diagnosis becomes acute. The two main types of cough which may be confused with an asthmatic cough are those of pertussis and of sinusitis.

Another type of cough due to inflammation of hypertrophied follicles of lymphadenoid tissue in the nasal and oral pharynx (especially after removal of the adenoids) is also very similar. This type of cough is diagnosed by inspection, particularly by nasopharyngoscopy, and is easily treated by irradiation of the hyperplastic and infected lymphoid follicles.

There is a certain similarity in the origin of the cough of asthma and of pertussis, in that both may result from the plugging of small air passages by mucus and the cough is relieved when the mucus is coughed up. In general, the allergic cough and that of pertussis may be differentiated by the following procedures: (a) therapeutic test—the cough of pertussis or sinusitis does not respond to sympathomimetic drugs; the allergic cough commonly does; (b) absence of eosinophilia in nasal and bronchial secretions in pertussis; (c) a high leukocyte count with a relative lymphocytosis is often characteristic of pertussis; (d) positive culture for H. pertussis in pertussis—this is especially important at the present time because of the routine practice of hypoimmunization against pertussis with highly effective vaccines which leads to situations for example where a child may cough briefly for a few days only, without whooping, and it would not be known that he had pertussis were it not for a positive culture; (e) no wheezing in pertussis on forced expiration as commonly occurs with an allergic cough; and (f) in pertussis the typical whoop commonly develops after about three weeks.

The sinus cough presents a special problem because sinusitis is so often concommitant with bronchial asthma. Both the sinus cough and the asthmatic cough are commonly worse at night, the asthmatic cough for unknown reasons, but the sinus cough occurs because in children the ethmoid sinuses are most commonly involved and in the prone position the discharge drains into the back of the throat causing cough as a result of irritation. Cough of sinus origin must be particularly suspected if it occurs when the child changes his position, especially during the day. This may occur, for example, when the child comes into the office for skin testing and lies down on the examining table for tests to be done on the skin of the chest.

Roentgenograms of the sinuses are often of considerable assistance but the best method of demonstrating infected sinuses is to examine the nose and the ostia of the sinuses. Too few nose and throat specialists are willing to spend the time necessary to examine the nose carefully and shrink down the mucous membranes fully in a frightened and uncooperative child, and the patient goes from one nose and throat specialist to another and from one allergist to another without relief. It is well for the pediatric allergist to train, so to speak, one capable nose and throat specialist of his acquaintance to careful examination of the sinuses in infants and children. For this purpose a specialist just starting practice, with unlimited time at his disposal and a desire to make good, will prove most satisfactory. His efforts will be well rewarded by the development of a technique which will enable the accurate diagnosis of sinusitis in infants and children, often missed by his older and less patient colleagues.

BRONCHOTETANY

This is a rare disease which may occur in children suffering from tetany when this disease affects the bronchial musculature. It was first described by Lederer[24] in 1913. He reported six cases in infants, all of which were fatal. The clinical symptoms consist of dyspnea, which may be severe, wheezing, use of the accessory muscles of respiration, dilatation of the alae nasi, and suprasternal and lateral costal margin retractions. Dullness may be percussed in some pulmonary areas with hyperresonance due to compensatory emphysema elsewhere. Bronchial breathing may be heard in some areas with various types of râles in other areas. A high fever may lead to the diagnosis of pneumonia. The roentgenographic diagnosis is commonly atelectasis. Rietschel[33] mentioned a case in an infant with recovery. Curschmann[10] reported a subacute case in a thirty-two-year-old man who had been repeatedly diagnosed as having bronchial asthma. Curschmann made a diagnosis of bronchotetany, and the patient was easily cured by the usual methods of treating tetany. He recommends that every young adult diagnosed as having bronchial asthma of unknown etiology be also studied for tetany.

In bronchotetany the administration of epinephrine hydrochloride is

contraindicated, as the symptoms are made worse thereby. The administration of calcium, particularly intravenously, is followed by brilliant results. It is the author's opinion that the beneficial results reported occasionally following the intravenous administration of calcium in asthma, which lead to its widespread use for this purpose some years ago, were probably obtained in patients whose pulmonary manifestations were the result of tetany rather than of bronchial asthma.

CARDIAC ASTHMA

The term "cardiac asthma" refers to severe attacks of dyspnea simulating asthma which occur in some individuals with cardiac failure from any cause, particularly left ventricular failure and tachycardia in cases of marked mitral stenosis. Attacks most commonly occur suddenly at night when the patient is sound asleep in the reclining position. Attacks may also occur on unusual efforts when awake. Unlike bronchial asthma, the injection of epinephrine aggravates the symptoms, and also unlike bronchial asthma, the best treatment is the injection of morphine.

Swineford and Magruder[37] appear to have confirmed the theory first advanced by Rackemann[31] that cardiac asthma is a form which heart failure of various types may take in an allergic or potentially allergic individual. Unger[40] on the contrary, believes that there is no particular relationship between allergy and cardiac asthma. I have been unable to find in the literature any reports of this condition in infancy and childhood. White* states that the youngest patients he has ever seen with cardiac asthma were eighteen and twenty-two years of age, respectively. He suggests that the reason the condition does not occur in the lower age groups is that although heart failure does occur in this group, both ventricles commonly fail together so that there is no unilateral strain on the right ventricle.

Dr. Samuel W. Clausen* has called my attention to the records of two children observed by him at the Strong Memorial Hospital, both of whom suffered typical attacks of cardiac asthma, a diagnosis reached after careful study and consultation with a cardiologist. One of these occurred in a girl eleven years of age as a complication of subacute hemorrhagic nephritis. She died of cardiac failure two days after the attack of cardiac asthma. The other patient was a boy twelve years of age who had attacks of cardiac asthma complicating acute hemorrhagic nephritis. He apparently made a complete recovery and was discharged from the hospital. The family left Rochester not long afterwards, and his subsequent fate is unknown.

BIBLIOGRAPHY

1. Aldrich, C. A.: Symptoms of vagotonia and thymic hypertrophy. J.A.M.A., 94:1119, 1930.
2. Anderson, D. H.: Cystic fibrosis of the pancreas and its relation to celiac disease. Am. J. Dis. Child., 56:344, 1938.

*Personal communication to the author.

3. Bradford, W. L., and Slavin, B.: Nasopharyngeal cultures in pertussis. Proc. Soc. Exper. Biol. & Med., 43:590, 1940.
4. Barach, A. L.: Inhalation Therapy. pp. 97, 102. Philadelphia: J. B. Lippincott Company, 1944.
5. Bray, G. W.: The asthmatic child. Arch. Dis. Childhood, 5:237, 1930.
6. Breese, B. B., Jr., and McCoord, A. B.: Vitamin A absorption in celiac disease. J. Pediat., 15:183, 1939.
7. Carr, J. L.: Status thymico-lymphaticus. J. Pediat., 27:1, 1945.
8. Chesney, J., and McCoord, A. B.: Vitamin A of serum following administration of haliver oil in normal children and in chronic steatorrhea. Proc. Soc. Exper. Biol. & Med., 31:887, 1934.
9. Clarke, J. A., Jr.: Method of eliciting musical râles. Presentation before the Society for the Study of Asthma and Allied Conditions at Atlantic City, April 30, 1938. Unpublished.
10. Curschmann, H.: Zur Frage der "Bronchotetanie" der Erwachsenen und ihrer Behandlung mit Kalzium. München med. Wchnschr., 61:289, 1914.
11. Dickey, L. B.: The pulmonary aspects of cystic fibrosis of the pancreas. California & West. Med., 57:41, 1942.
12. Dutton, L. O., and Fuchlow, R.: Quoted by Forman, J.: A review of allergy. Ohio State M. J., 41:522, 1945.
13. Farber, S.: Pancreatic insufficiency and the celiac syndrome. New England J. Med., 229:653, 1943.
14. Glaser, J., and Landau, D. B.: The prophylaxis of allergic disease. J. Pediat., 8:470, 1936.
15. Glaser, J.: Pediatric allergy, a critical review of recent literature. Ann. Allergy, 3:373, 1945.
16. Hansel, F. K.: Allergy of the upper and lower respiratory tracts in children. Ann. Otol., Rhin. & Laryng., 49:579, 1940.
17. Ingals, E. F.: Respiratory movements of the bronchial tubes. J.A.M.A., 45:1302, 1905.
18. Irich, H. E.: Dosage of camphorated tincture of opium and morphine for infants. Am. J. Dis. Child., 49:1503, 1935.
19. Jackson, C., and Jackson, C. L.: Bronchoscopy, Esophagoscopy and Gastroscopy. Ed. 3, p. 64. Philadelphia and London: W. B. Saunders Company, 1934.
20. Kahn, I. S.: Essential differences in chronic pollen hay fever and asthma in children and in adults. J. Lab. & Clin. Med., 12:1197, 1927.
21. Kern, R. A.: Prophylaxis in allergy. Am. Int. Med., 12:1175, 1939.
22. Kopp, cited by Riesman, D., and Harris, S. F., in Christian, H. A., and Mackenzie, J.: Oxford Medicine. Vol. 4, p. 52. New York: Oxford University Press, 1928.
23. Laurens, H.: Mechanisms of respiratory movements. In Brennemann: Practice of Pediatrics. Vol. 2, Ch. 38, p. 19. Hagerstown, Maryland: W. F. Prior Company.
24. Lederer, R.: Ueber "Bronchotetanie," ein noch nicht bescribenes Krankheitsbild der Spasmophilie. Ztschr. f. Kinderh., 7:1, 1913.
25. Manges, W. F.: Diagnosis of non-opaque foreign bodies in the air passages. Am. J. Roentgenol., 9:288, 1922.
26. Maytum, C. K., and Willius, F. A.: Abnormal respiration of functional origin. Proc. Staff. Meet., Mayo Clin., 9:308, 1934.
27. Maytum, C. K.: Sighing dyspnea, a clinical syndrome. J. Allergy, 10:50, 1939.
28. Olivier, E.: Anatomie Topographique et Chirurgie du Thymus. Paris: Steinheil, 1911.
29. Prince, H. E., in discussion on Browning, E. H.: The differentiation of bronchial asthma from sighing dyspnea and cardiac asthma. South. M. J., 35:914, 1942.
30. Prince, H. E.: Personal communication to the author.
31. Rackemann, F. M.: Clinical Allergy. Pp. 415-420. New York: Macmillan Company, 1941.
32. Ratner, B.: Certain aspects of eczema and asthma in infancy and childhood from the standpoint of allergy. M. Clin. North America, 6:815, 1923.
33. Reitschel, H.: Bronchotentaie, Bronchialasthma, und asthmatische Bronchitis im Säuglingsalter. Monatschr. f. Kinderh., 12:261, 1914.
34. Silberberg, M.D.: Sighing dyspnea and the hyperventilation syndrome. M. J. Australia, 2:39, 1942.

(Continued on Page 462)

SOME PROPERTIES OF ANTIGENS AND ANTIBODIES

SANFORD B. HOOKER, M.D., F.A.C.A. (Hon.)
Boston, Massachusetts

ONE important consideration influenced my choice of this topic Large associations of allergists must not only have constructive policies regarding educational, technical, and ethical qualifications for their membership but, for progress, there must be concerted and systematic plans for investigating the basic properties of the multifarious substances to which man and animal become allergic, and the nature of the serological and cytological responses of the "host" to these substances.

In explanation of this use of the words "concerted" and realizable "progress," I state my conviction that, for example, productive investigations of the allergenic properties of ragweed-pollen will be more economically and fruitfully conducted by an assembly of trained, interested, well-furnished, and well-advised youngish scientists—such teams as have recently proved their ability in the fields of radionics and nuclear or plasma fission—than if left to semi-isolated, inadequately equipped individuals, however earnest and industrious and intelligent they may be. With some notable exceptions the young prepared mind is more labile, more roving, more readily catalyzed by actual experimental manipulations and observations at the bench than the old mind, which is more likely to be canalized and irreversibly coagulated. But we should not forget the old French aphorism *"Si la jeunesse savait, si la veillesse pouvait."* Elders can often diminish misspent time and effort by avoiding excursions along dead-end trails, and, in general, should have a keener appreciation of the indispensability of controls—an innate, ingrained, or imposable realization that in any experiment all variables but one should be stabilized whenever possible.

Now, terminating these somewhat pedantic and ponderous pontifications, and attempting furtherance of a more quickly penetrating analysis of many immunochemical problems confronting allergists, I venture again to mention in this review some fundamental properties of antigens and antibodies that need constantly to be kept in mind by planners and experimenters and interpreters in this field.

The numerous and well-consolidated advances made during the past twenty-five years are attributable to an unusually rapid increase in the number of investigators who have learned and applied physicochemical concepts and methods to the problems of immunology; and, in great measure, attributable to the increasingly pervasive influence of the outstanding worker in the field, Karl Landsteiner. His interest in the intimate chemical nature of antigenic specificity was vigorously sustained

From the Evans Memorial and Massachusetts Memorial Hospitals, and the Boston University School of Medicine.
Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

for decades; his unremitting industry, his original and penetrating ideas, his thorough experiments and rigorously tested conclusions have not only enriched our knowledge but have opened many paths for other investigators to explore. Even a superficial review of Landsteiner's studies of natural antigens, haptens, and artificially compounded proteins would exhaust the time at my disposal; and it would be superfluous since they are described with his many other contributions in his posthumously published (1945) monograph, "The Specificity of Serological Reactions," which includes an amazingly complete critique of the pertinent literature. This revised edition is nearly doubled in content and has been thoroughly, laboriously, and lovingly edited, chiefly by one of his closest pupils, Merrill Chase.

Nor is there time for any historical review of the subject, formally opened by Arrhenius in his lectures on immunochemistry in 1904 at Stanford University. The present widespread interest and activity are too recent to permit a dependable evaluation of the numerous contemporary contributions, but I must name Heidelberger and Kendall, who, from the starting point established by Wu, have expanded methods of analyzing specific precipitates, a signally important advance in the quantitation so necessary for real immunochemical progress.

The few topics I have selected, primarily by way of illustration, because it is impossible here to be exhaustive, are not necessarily the most important but are naturally the ones with which my work has made me the more familiar. Some have an obvious, others only a remote bearing on allergic mechanisms. Many aspects are unsettled and obscure, and much that I shall say will be frankly speculative. It must be clearly understood that we really know but little of the detailed composition of proteic antigens and practically nothing of the intimate chemical structure of antibody; in Landsteiner's words, "No finished theory of serum reactions has been attained comparable to those which cover, and make it possible to formulate, the ordinary phenomena of chemistry."

In order to render the discussion intelligible to those unversed in immunological nomenclature, it is desirable to define a few rudimentary terms.

ANTIGEN AND HAPTEN

Antigens are *soluble* substances that stimulate the formation of, and react specifically with, antibodies. They are usually of high molecular weight and must be *blood-foreign* (heterozoic) but not necessarily body-foreign (c.f., the antigenicity of autogenous casein and lens-substance) to the animal to which they are administered. Sometimes antigens are effective by inhalation, ingestion, or inunction, and these routes of entry are important in the initiation and maintenance of allergic conditions, but antigens are experimentally most active when introduced more or less directly into the circulation. As a rule, antigens are proteins, although some complex polysaccharides and lipins are antigenic.

Haptens, by Landsteiner's definition, are *separable* components of many complex antigenic materials, including bacterial and other cells, and they include innumerable, relatively simple chemical compounds which can condition specific reactivity but lack a truly antigenic power or possess it in a restricted degree. For example, a glycoside may be coupled with a protein and the compound will incite the production of antibodies whose specificity depends upon the structure of the glycoside. The separate glycoside reacts specifically with the immune serum but does not have any immunizing property; it is not antigenic, it is a hapten. A group of neighboring atoms known to be important in specific reactions, but not necessarily separable from the whole molecule, may be called a *determinant* of specificity. In illustration, the type I pneumococcal polysaccharide, "soluble specific substance," in the (deacetylated) form in which it was first prepared, is a hapten. In its isolated state it is feebly or not at all capable of inciting antibody-formation in some kinds of animal, but it is specifically precipitable with the homologous type I pneumococcal antiserum (not all haptens react visibly with antibody; they may only specifically *inhibit* an otherwise expected subsequent reaction with a precipitable form of antigen or hapten). When the polysaccharide is coupled with protein it is powerfully antigenic. When acetylated it becomes antigenic and then *in vitro* is capable of removing more antibodies from an antiserum for whole pneumococci than is the deacetylated polysaccharide. Here, the acetyl group may be referred to as a subdeterminant. This illustration introduces the conception of multiple antibodies developed in response to qualitatively diverse determinants on single antigenic molecules, which will be discussed later.

ANTIBODY

This awkward and ill-conceived word is defined, circularly, as the specific substance evoked by the antigenic stimulation of animals. Knowledge of an analogous response of vegetables is altogether too insecure to be discussed here. Antibody is a minutely but specifically modified globulin built up within tissue cells under the orientative or organizing influence of antigen. The mechanism of antibody formation is a major immunological problem. That antibody can be produced in a test tube has been frequently affirmed, and processes were even patented many years ago, but the evidence is unconvincing. Antibodies are a product of living cells, and many indices have long pointed most definitely to the cells of the reticulo-endothelial system—the clearing houses of the blood—as the important primary participants in this fundamentally specific protective function. During the past ten years there has accumulated a good deal of evidence that lymphocytes also play a prominent rôle.

Of early theories of antibody formation the only one here mentioned was exhumed and re-interred some years ago. Because of the specifically interreactive correspondence of antigen and antibody, it was assumed—

for some reason entirely incomprehensible to me—that a molecule of antigen, or a specific fragment of it was incorporated in the antibody. Buchner temporarily embraced this theory, but soon rejected it because of the huge disproportion between the large amount of antibody formed and the tiny amount of antigen which would evoke it, such as 100,000 neutralizing units from one unit of toxin.

Some years ago there was a rather fantastic, or perhaps clairvoyant, attempt to remove the quantitative objection by postulating a "hybridization" or "depolymerization" or "multiplication" of the antigen. Dr. Boyd and I interposed a serious mathematical obstacle to this theory and later offered the following seemingly incontrovertible quantitative evidence against it. If the reactive groups (antideterminants) of antibody are derived from the antigen, then each combining site must contain at least part of a specific antigenic determinant. In a compound antigen prepared by coupling arsanilic acid with protein, each determinant must contain arsenic, and the molecule of corresponding antibody should also contain at least one atom of arsenic if the Buchnerian theory be correct. Consideration of the experimental quantitative relationships of atoxylazo-casein with an immune serum for atoxylazo-egg-white allowed us to conclude that the theory would demand the presence in the immune serum, of at least several hundred or, more probably, several thousand times as much arsenic as is easily detectable by chemical test. None was found; from which it follows that the essential specific determinant of the antigen does not permanently enter into the structure of the combining group of the antibody, but acts rather like a catalyzer.

The extraordinary specificity of the serological reactions of some substances of known structure indicates the fundamental importance of the parts played by spatial configuration and distribution of intermolecular forces in localized areas on the molecules of antigen, hapten, and antibody. The striking ability of animals to synthesize faithfully reflective antideterminants allows us deliberately to produce relatively specific reagents for almost any fairly simple or highly complex organic compound. Mudd has assumed the antideterminant to correspond stereochemically with the antigenic determinant because the structural units, amino acids and peptides composing a restricted area of the globulin-molecule, are arranged and united under the selective orienting influence imposed by a similarly restricted area of any antigenic molecule that happens to be contiguous. Only such structural units are used as can conform with the electrical and structural specifications characterizing the patterned template closely apposed to the nascent globulin-molecule. When the molecule of specifically modified globulin is finished, dissociation is assumed to take place, and the template, as in ordinary practice, can be used again and again.

Pauling has re-emphasized this idea of complementariness and has proposed a theory that assumes the order of amino acids in the poly-

peptide chains to be the same as in normal globulin; a portion of the chain merely coils up differently and forms a local pattern in complementary configurational correspondence with the determinant on the antigen.

When visualizing these hypothetical processes, it appears that the molecule of antibody might have but a single combining site; at least the immunochemical valence should be small and would probably not be the same on different molecules.

To account for the continued formation of antibody after injections of antigen are stopped, and to explain the "anamnestic" phenomenon, i.e., the renewed production of antibody to a formerly administered antigen when a new one is injected or a new stimulus is applied (India ink), these theories must suppose that some antigen remains available to antibody-forming cells much longer than has hitherto seemed probable, excepting perhaps the special case of viral antigens whose habitat is intracellular. However, Rous found certain iron-containing compounds to remain for months in Kupffer's cells, which could be massaged into the blood stream and magnetically collected because of their iron content; this evidences the longevity of this kind of reticulo-endothelial cell, and hints at a method of experimental attack.

Whatever may be the intimate mechanism of their formation it is certain that antibodies are proteins. They are invariably associated with the globulins of immune sera and they have not been dissociated from these proteins although much of the globulin-molecule can be digested away with little impairment of specific reactivity. There is no acceptable evidence that "antihaptens" or combining groups are separable from antibody as are haptens from some antigens. The amount of serum-globulin is commonly increased by intensive immunization. In its response to denaturing influences, to proteolytic enzymes, and to other manipulations, antibody parallels the behavior of protein. It can be relatively freed from mixture with other constituents of serum or tissue juice by salting out, by treatment with alcohol, acetone, or various adsorbents, by cataphoresis, and by dissociation of specific antigen-antibody precipitates. There have been reports that metallic salts and dissociates of pneumococcal antibody were 100 per cent precipitable by antigen, no protein being left in the supernate; and Northrop has produced crystalline diphtheric antitoxin.

ANTIGEN-ANTIBODY REACTIONS

Although salting-out and electrophoretic patterns establish certain coarse differences, it is difficult or impossible to distinguish one antibody from another or from normal globulin by the ordinary methods of chemistry. However, this may be accomplished with great ease and precision by serological reactions. Different techniques reveal reactions of various kinds and the descriptive terms applied to reactions involving precipitation, agglutination, neutralization, et cetera, have been adapted to define

the antibody concerned. The different names, precipitin, agglutinin, et cetera, have tended to imply that the antibodies are also different, but the "unitarian" hypothesis sponsored by Dean and by Zinsser has been firmly upheld and it may be confidently accepted that a single determinant group, not necessarily a single antigenic molecule, leads to the production of a single kind of antibody, the complexity of whose combining group, however, may vary considerably around a main pattern; the superficially different reactions depend merely on the different conditions of test. But there are many antigens in bacterial and other cells, in serum, egg-whites, pollens, et cetera, and a lot of time has been wasted in using such mixtures inappropriately; it must again be emphasized that only pure, molecularly homogeneous antigens should, if possible, be employed in studies of the kinetics and many other theoretical aspects of immunochemistry. I cannot here describe the various types of serological tests; the precipitin reaction will be used as the simplest illustration.

Since the early studies of Bordet it has long been accepted that the antigen-antibody reaction may be divided into two stages: primary combination, which is surely specific, immunochemically; and secondary flocculation, which until recently has been considered non-specific by nearly all investigators.

PRIMARY STAGE OF COMBINATION

When antigen and antibody are mixed in equivalent proportions their actual combination (of whole molecules, not fragments) is demonstrated by the disappearance of both reactants from the supernate and their quantitative recovery in the washed precipitate; the reaction is not one of simple catalysis. The combination is firm but at least partly reversible, and there is no splitting or digestion as a direct result of union. Combination is almost instantaneous, probably as a result of Brownian motion which, at room temperature in the case of molecules the size of antibody, has a calculated velocity of 0.5 meter per second. Thus, between the billions of molecules of antigen and antibody in even a dilute mixture, the number of immediate and effective impacts must be enormous.

The molecules of antibody and proteic antigens behave like fairly rigid ellipsoids of greater or less eccentricity.

Analyses of specific precipitates have shown that their composition varies with the original concentration of the reactants; that is, combination can take place in varying proportions. This argues for the presence of multiple binding-groups on at least one of the kinds of molecules involved. That multiple determinants exist on the antigen is suggested by the relatively poor precipitability of compound antigens that contain only a few haptens. We found that atoxylazocasein (casein-azo-arsanilic acid) was no longer precipitable if the number of atoxyl groups was reduced below about thirteen per molecule. There is no precipitation with simple dispersed haptens that possess only one binding group.

Concerning the molecule of antibody, there is no convincing evidence for the existence of many separate sites of combination. It is certain that many more molecules of antibody can combine with one of antigen than vice versa. The conditions we imagine to exist at the site of formation of antibody are probably not such as would favor the building up of many combining groups. In our published appraisal of current evidence relating to immunochemical valence, the minimal figures for antigens ranged from 5 (ovalbumin) to 230 (hemocyanin); the megamolecule of tobacco-mosaic virus probably has an even higher number of combining groups. In sharp contrast, ordinary antibody seems to be univalent although there is a little uncertain indication of divalence.

IMPORTANCE OF SURFACES

One still current notion of the antigen-antibody reaction is that the antigenic molecules, particles, or cells become more or less plastered with a layer of antibody-globulin, and many properties of these primary aggregates are those of the outer surface of this envelope. The conditions leading to the formation of this envelope as well as subsequent developments are importantly influenced by the properties of surfaces. The molecules and particles with which serology mostly deals lie within the range of size to which the rules of colloidal chemistry often apply. Analogies include combination in varying proportions, importance of electrolytes, slow reversibility, and the existence of optimal and zonal reactions so readily shown by the precipitation of gum-mastic with ferric hydroxide sol. From what we know of the shape, dimensions, weight, and composition of proteic molecules it appears that their atomic components and peptide chains are so close together that no molecule larger than the lower fatty acids could pass through the outer layer of a molecule of protein. Certainly the structure seems too rigid and densely packed to allow the entry of the relatively enormous molecules of antibody-globulin. A further reason for considering that the internal atomic components of either antigen or antibody-molecules have little if anything to do with immunochemical combination is the fact that the attractive potency of the various intermolecular combining forces diminishes very rapidly with increase in distance between the reactants. That of the strongest, primary valence, varies inversely as the square of the distance. That these Coulomb forces, attractions between positive and negative charges, e.g., between amino and carboxyl groups, are sometimes operative in antigen-antibody unions may be inferred from the strong influence of polar, especially acidic, groups upon specificity. But in many more instances it is highly probable that secondary valences are involved, either exclusively or in addition to an ionic mechanism. Such types of bond—van der Waals' forces, dipole-ion, magnetic forces between dipoles, and the hydrogen bond—are very much weaker than primary valence and vary inversely as the fourth or higher power of the distance.

Therefore, reactive groups must be closely apposed and our concern is largely with surface or adsorptive forces. Thus our problems are simplified because there is less of the molecule for us to study and we may thereby avoid some of the terrifying complexities that the students of atomic nuclei have encountered.

Other pertinent observations are that only the *outer* shells of electrons possessed by atoms are reactive in the ordinary chemical sense; the *distal* portion is prominently effective in substituents attached to proteins by the diazo linkage, e.g., groups in the *para* position in ring compounds; the *terminal* amino acid dominates the specific reactivity of dipeptides or even pentapeptides; the important chemical, and immunochemical, distinction between glucose and galactose centers around the fourth carbon atom which is *outermost* in the ring structure of the hexose portion of the coupled glycoside. These outer groups may be more strongly polar and/or less liable to steric hindrance. They may fit more firmly into a pocket formed by specific invagination of an area on the surface of the antibody-molecule. In bacteria, or red cells, too, the ectoplasmic or stromal antigens are controllingly influential.

The configuration of surfaces is obviously determinative in crystallization. It has been observed that such atoms or groups as are mutually replaceable in crystals are immunologically equivalent, e.g., the halogens and the methyl group if they occupy the same position on the benzene ring. The salts of H_3AsO_4 and H_3PO_4 are isomorphous and different from those of H_3SbO_4; likewise arsanilic and phosphanilic acids, as haptens, are mutually cross-reactive, whereas stibanilic acid is dissimilar. Neither glucose and galactose nor the α- and β-glucosides form mixed crystals and these compounds are immunochemically differentiable.

Another property of crystals furnishes a striking illustration of the decisive importance of spatial configurations. Diamond, but not graphite, adsorbs methylene blue; the reverse occurs with succinic acid. The only fundamental difference between these elementally pure adsorbents lies in the different spacing of the carbon atoms.

In comparing molecular weights, or surfaces, of antigens with the ratio of antibody to antigen in specific precipitates, Boyd and I observed a fairly parallel relationship. Substances ranging in molecular weight from perhaps about 4,000 up to 8,000,000 fell approximately upon the calculated curve as shown in the figure presented. These results are compatible with the assumption that, in the zone of equivalence, the molecule of antigen is about completely covered with a single layer of antibody-globulin molecules. The antigenic or haptenic molecule or particle is regarded as the nucleus upon which antibody is deposited and is the center of each primary aggregate. The absolute area of the molecular surface could not be the sole determining factor unless the surface were fairly well and evenly studded with active determinants corresponding with the individual antibodies being tested. Observed

ratios are sometimes lower than the calculated ones, possibly ascribable to an inadequate number or uneven spacing of combining sites, nonhomogeneous dispersion of antigen (aggregation would result in a lower ratio) hindrance from flattening of attached molecules of antibody, and the relative concentration and dissociability of different grades in the particular serum examined. There are many evidences for the existence of different kinds of antibody-molecules in a given serum, ranging from those that most perfectly reflect the fields of force in the determinant to the weakest kind with a combining group so incomplete as barely to permit a recognizable union with its antigen. Diphtheric antitoxins vary widely in speed of flocculation, firmness of union, and therapeutic value.

It is not known whether the powerfully poisonous parts or areas of the molecule of diphtheric toxin are actually the antigenic determinants with which diphtheric antitoxin combines. In seeking a solution to this problem, I reasoned that if enough foreign haptenic groups could be linked with the toxic protein then an antihaptenic serum totally unable to react with unmodified toxin might still neutralize the coupled toxin by a merely mechanical covering of its surface. Tests involving arsanilic acid as hapten and antihemocyanin-azo-arsanilic acid as a potentially neutralizing serum led to equivocal results. The frustrating difficulty appeared to be a chemical destruction of toxicity when a number of groups calculated to be surely enough to allow complete coverage by antihapten was combined with the toxic molecule. Perhaps other methods of coupling may overcome this difficulty.

There has been recorded one instance of passive protection against actual infection, by an antiserum for an artificial antigen containing a purely synthetic hapten. Goebel coupled normal equine globulin with cellobiuronic acid (a disaccharide containing one molecule of glucose and one of glycuronic acid) and obtained an antiserum capable of protecting mice against infection with virulent pneumococcal strains of types II, III and VIII. This feat would have seemed impossible not many years ago.

SECONDARY STAGE OF FLOCCULATION

When particulate or dissolved antigen is mixed with an appropriate amount of antibody, aggregates are formed and more or less promptly grow to visible size and then settle out of solution. According to one theory, the primary antigen-antibody particles, because of the surface-deposit of "denatured" antibody-globulin, behave nonspecifically as a salt-sensitive colloidal suspension. It has long been known that the presence of an electrolyte is prerequisite for flocculation. That the specific-globulin portion of the antigen-antibody complex is importantly concerned in flocculation, is indicated by the parallel electrophoretic behaviors of particles of heat-denatured globulin and particles of antigen coated with antibody (Shibley). Further cogent evidence is afforded by the

influence of sensitization upon bacteria of different isoelectric points; as the cells become more and more thoroughly coated with antibody the isolectric points of the aggregates converge toward a common value which is that of globulin (Mudd). We may assume this to be an example of the "wisdom of the body": specific precipitates, probably allergen-antibody complexes, and, notably, specifically sensitized bacteria are very readily engulfed by phagocytic cells; thus nature economizes on the number of mechanisms necessary for the disposal of invasive antigens of many kinds and many different characteristics.

IS AGGREGATION SPECIFIC?

Marrack has diagrammed the unions of antigen and antibody; in the zone of equivalence the aggregate is represented as a three-dimensional lattice in whose structure molecules of antigen and antibody alternately participate. This directly implies that the secondary phase of flocculation or agglutination is just as specific as the primary combination of the two reactants. I have mentioned the evidence that, in the equivalence-zone and especially in the zone of antibody-excess, each molecule of antigen is nearly or completely covered by antibody-globulin and so, being blocked off, would have no opportunity to serve as an intermediate link in the building up of any lattice-structure. There are a number of arguments and experimental results pro and con the specificity of serological aggregation, but the subject is not of immediate or primary interest to allergists and the ground is still hot from the fires of controversy, so I hasten to step off, with the remark that controversy is a foe of stagnation, a spur to the imagination, and not infrequently a source of progress as well as amusement.

DIFFERENT DETERMINANTS OF ANTIGENIC SPECIFICITY ON SINGLE MOLECULES

In order to explain cross-reactions among related kinds of bacterial antigens, Durham supposed the bacterial cell to be made up of a mosaic of several antigens, some of which are possessed in common by related strains. Many other natural substances—serum, egg-white, pollen, dander—are likewise antigenically and allergenically complex. The idea has been amply confirmed, and extended to apply to purified proteins. This multiple-determinant hypothesis is obviously of interest and of practical significance to the student of antigens and allergens. If qualitatively different groups exist on single molecules of antigen and give rise to respectively specific and molecularly separate antibodies, then the analyst will be confused and frustrated if he attempts to isolate these antigenic substances by using any method of separating different kinds of molecules.

I have reviewed this topic at tiresome length elsewhere and shall here mention only a few examples. Partly iodized horse-serum evokes one kind of precipitin that reacts with iodized chicken-serum, and another

that reacts with unmodified horse-serum; the first reflects the determinant-group containing iodine (because the two animal proteins are antigenically independent save for their content of the Forssman substance), and the second shows that some species-specific determinants still remain on the iodized protein. My own interest in the problem was aroused during a study of another synthetic antigen, gelatin-diazo-arsanilic acid. The non-antigenicity of gelatin has been attributed to a deficiency in aromatic amino acids. The formation of azoprotein dyes is certainly in part mediated through the amino acids tyrosin and histidin. "Complete" proteins contain both; gelatin is deficient in tyrosin. In comparing anti-azogelatin with anti-arsanilic-azo-egg-white it seemed possible that their different properties might be accounted for by assuming that the former contained only the antibody or antihapten which corresponded with histidin-diazo-arsanilic acid. Tests with diazonium compounds of the acid with phenol and iminazol, the respective cyclic nuclei of tyrosin and histidin, supported the assumption.

Still, these artificially conjugated antigens might be only a special case, so further tests were made with related natural antigens, crystalline ovalbumins from the hen and duck. Again evidence was obtained which indicated that these proteins, rigorously tested for molecular homogeneity, possess properties leading to the formation of different and individually specific as well as similar common antideterminants.

The cross-reactivity of the polysaccharides of *B. friedlanderi*, type B, and pneumococcus, type II, is similarly indicative. Even more striking is the haptenic specificity of the β-glycosides of glucose and galactose in comparison with α- and β-glucosides. Here are revealed the *co-existing* specific groups that center about the configurations surrounding the fourth carbon atom of the ring, and the *cis* or *trans* position of the prosthetic group attached to the first carbon atom.

The discussion of this topic may be summarized in the statements that molecularly homogeneous antigens can stimulate the formation of molecularly separate and qualitatively different antibodies; and there is strong evidence that this should be ascribed to different submolecular surface-components of the antigen.

DEVELOPMENT OF WIDENED REACTIVITY OF ANTIBODY

It is a general characteristic of antibodies that they are more specific when obtained after a short course of immunization with relatively small quantities of antigen. As the number of injections increases, the antiserum tends to become more and more cross-reactive. This has clearly been shown with crystalline ovalbumins from the hen and duck as well as with many related groups of bacteria.

A rather striking and instructive example of this phenomenon was revealed in experiments involving the specific inhibitive properties of such haptens as (*p*-amino) benzoic acid (PABA) and cyclo-hexane car-

boxylic acid (CCA) which contain the same kinds of atoms and have a strong structural resemblance to each other.

Immune sera were derived from rabbits that received repeated courses of injection of *limulus* hemocyanin coupled with *p*-amino-benzoic acid by the diazo linkage. The test-antigen was casein-azo-PABA, the proteic

TABLE I.

ANTIHEMOCYANIN-PABA + CASEIN-PABA INHIBITED BY SIMPLE HAPTENS									
	PABA			BENZOIC ACID			CYCLOHEXANE CARBOXYLIC ACID		
	MICROMOLS REQUIRED TO INHIBIT COMPLETELY FOR								
BLEEDING	1	2	3	1	2	3	1	2	3HR
2D	.17	.17	.26	.39	.59	.59	NOT BY		2.00
3D	.08	.12	.17	.08	.17	.26	.12	.39	.59
5TH	.08	.17	.26				.12	.17	.26

carrier of the hapten being antigenically quite different from hemocyanin, so that positive serological reactions between these reagents can confidently be attributed directly to the specific properties of the haptenic group (and closely neighboring structures of the protein to which it is attached). An optimally reactive concentration of test-antigen was mixed with 5 per cent fluid gelatin and chilled in small-bore tubes. Appropriately diluted antiserum and serially diluted haptens resembling PABA were mixed, stratified on the solid gelatin-antigen preparation, and incubated at 37° C for five hours. Positive and negative reactions at the sharp interface ensured by this technique (Hanks) were recorded at hourly intervals. PABA, and sufficiently similar compounds in adequate concentration, would completely inhibit precipitation for twenty-four hours or longer. The haptens in the strengths used did not prevent precipitation in unrelated systems, i.e., the inhibition was specific.

The data in Table I exemplify the principle that the degree of immunization determines the range of reaction. It is apparent that a small quantity of PABA with serum from the second bleeding is completely inhibitive for an hour whereas a twelvefold greater amount of CCA is ineffective. This marked disparity has almost disappeared when the same test is applied to serum from the fifth bleeding. This indicates that the relatively simple, specific, and probably small pattern of the antideterminant (combining group) on the molecules of antibody-globulin formed early in the course of immunization, has been elaborated by continued antigenic stimulation into an active patch that is more com-

plex, less narrowly specific, and probably larger than the combining groups originally formed. The latter pattern may be supposed to be made up of more numerous reactive points permitting a closer adaptation to a number of antipodal electronic points on a heterologous hapten sufficient to result in firmer combination, with a dissociation-constant low enough to delay for an appreciable period the still firmer union of antibody with the visibly reactive test-antigen.

From these same data another deduction of considerable interest may be drawn. Early antibody was inhibited by homologous PABA but not by CCA; however, later antibody was temporarily, but completely inhibited by CCA, which would not have been the case had an appreciable quantity of early antibody been retained in the rabbit's circulation during the interval between bleedings. This indicates a virtual disappearance of early, more specific antibody and its replacement with kinds capable of reaction with heterologous haptens. Through the use of radioactive isotopes it has been possible to estimate that the half-life of antibody-molecules is about two weeks; inasmuch as seven weeks of injections had elapsed between the second and third bleedings of the rabbit that produced the antihemocyanin-azo-PABA there was ample time for the changes mentioned to have taken place.

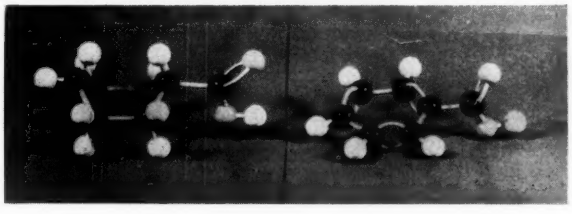

Fig. 1

In their gross atomic anatomy, PABA and CCA bear a marked resemblance to each other; in attempting to explain the results observed we must consider the possible influence of the finer configurational differences between the two compounds which can be seen in the molecular models of benzoic and cyclohexane carboxylic acids contrasted in Figure 1. I can do little more than list the dissimilarities: The planarity of the ring in benzoic acid is a feature not shared by CCA, in which, because of the different angles between the carbon atoms, the ring in profile may resemble either a cradle (as in the model shown) or a rocking chair; the N = N group in the coupled PABA might constitute part of a combining pattern that could not be matched by the simpler CCA; the CCA compound occupies more space because of greater distance between the hydrogen atoms attached to its ring; the presence and position of double bonds in cyclic structures (as in PABA) can definitely influence specific com-

(Continued on Page 467)

ROLE OF DERMAL NONATOPIC SENSITIVITY (TUBERCULIN-TYPE SENSITIVITY) IN CONTACT DERMATITIS

Preliminary Report

STEPHAN EPSTEIN, M.D., F.A.C.A.
Marshfield, Wisconsin

IT is customary to distinguish two forms of dermatitis or eczema caused by allergy.

1. *Atopic dermatitis,* based on hypersensitivity of the vascular connective tissue layers. The allergic response of the skin is of the anaphylactic type, namely, an immediate whealing reaction to scratch or intradermal tests. This sensitivity is often referred to as dermal sensitivity, to differentiate it from the next form of dermatitis.

2. *Contact dermatitis,* based chiefly on epidermal hypersensitivity. The allergic response of the skin is of the delayed eczematous type, namely, a delayed inflammatory, eczematous and vesicular reaction to a patch test.

The following presentation will demonstrate that dermatitis from direct contact may also be based wholly or in part on a third form of skin sensitivity, namely, dermal nonatopic hypersensitivity, as manifested by a delayed inflammatory tuberculin-type reaction.

Dermitis: A form of dermatitis based on dermal nonatopic hypersensitivity.

Several cases of dermatitis from external contact with chemicals were studied, in which patch tests with the causing allergens were negative, whereas intradermal tests with weak dilutions of the same substances produced intensive delayed tuberculin-type reactions. Clinically, the dermatitis appeared to be the picture of a localized papular dermatitis in one instance, a localized eczematous eruption in others, a severe eczematous dermatitis with generalized id-like characteristics in a further case, and a "dysidrotic" eruption in another instance. The causative chemicals were rivanol, nickel and penicillin-G.* Microscopic sections both from the site of the dermatitis and from test sites demonstrate severe dermal inflammation with or without associated epidermal changes.

The role of nonatopic dermal hypersensitivity in contact dermatitis.

Allergic investigation by means of patch and intradermal tests of cases of allergic contact dermatitis (epidermitis), notably those cases due to nickel and chromates, but also due to other substances, reveals the presence of dermal nonatopic hypersensitivity. This is manifested by a delayed tuberculin-type reaction at the site of the intradermal test, in addition to an eczematous response to the patch test. The severity of the dermal reaction may or may not parallel the degree of the epidermal reaction.

From the Marshfield Clinic and St. Joseph's Hospital, Marshfield, Wisconsin.

*This latter case was described previously.[1]

The lesions in this type of dermatitis not infrequently present characteristic clinical features; namely, a tendency to localized and more infiltrated patches.

A peculiar phenomenon in attempts at passive transfer of dermal nonatopic sensitivity.

Attempts at passive transfer in cases of contact dermatitis based wholly or partially on dermal nonatopic sensitivity were uniformly unsuccessful. However, when serum was injected into the skin of another person who was sensitive to the same agent, the following observation was made: Normally such serum would not produce any reaction in the recipient. However, if a patch test or intradermal test had been performed recently on the donor, the serum of the donor in several instances produced a delayed tuberculin-type reaction in the recipient. The circumstances of these experiments indicate that other factors operate in addition to transmission of the original allergen through the donor's serum.

Identity of dermal nonatopic sensitivity and tuberculin-type sensitivity. Its relation to contact-type epidermal sensitivity.

The existence of dermal sensitivity in contact dermatitis, especially in cases due to nickel, chromates, and arsphenamine, has been known for a long time, although its importance in regard to the clinical manifestations was usually overlooked.

The dermal nonatopic sensitivity, as described above, cannot be distinguished from the tuberculin-type reaction. There are several factors which speak for their identity.

The relationship between this dermal nonatopic sensitivity to the eczematous epidermal sensitivity of contact dermatitis is not clarified. They may represent two essentially different forms of sensitivity or perhaps may be immunologically identical and different only in regard to the shock organ.[1] This dermal nonatopic sensitivity apparently plays a much greater role in contact dermatitis, especially from sulfonamides and penicillin, than has been previously recognized. This has an important practical implication. Patch tests alone may fail to demonstrate sensitivity to therapeutic agents and other contact allergens. When intradermal tests with these substances are performed, it is necessary to use weak solutions to avoid serious reactions.[1]

The dermal nonatopic sensitivity must be distinguished from the anaphylactic or atopic, urticarial type of dermal sensitivity. There is no proof as yet for the claim that anaphylactic and tuberculin-type sensitivity are only two forms of the same immunologic process. However, it should not be denied that these two types are also frequently encountered in the same patient. Tuberculin-type sensitivity, especially to bacterial antigens, frequently is an important factor in the clinical manifestations of certain forms of so-called atopic dermatitis.

REFERENCE

1. Epstein, Stephan, and Pinkus, Herman: Penicillin dermatitis based on tuberculin-type sensitivity. Ann. Allergy, 4:186, 1946.

PRINCIPLES AND PRACTICE OF AEROSOL THERAPY OF THE LUNGS AND BRONCHI

HAROLD A. ABRAMSON, M.D., F.A.C.A.
New York, New York

IT IS indeed a pleasure to address this meeting of the American College of Allergists on the subject of Aerosol Therapy because it provides an opportunity to bring into the sphere of the College some of my wartime experiences in the Office of the Chief, Chemical Warfare Service, in connection with the principles and practice of aerosol therapy of the respiratory tract.

It may not be generally known to the physician that the subject of aerosols or mists was of extreme importance to the Chemical Warfare Service, not only because of the possibilities inherent in the use of therapeutic aerosols of the type which enters this discussion, but also because aerosols were of significance in many other aspects of chemical warfare. For example, screening smokes are aerosols. In the production of screening smokes, whether by means of condensed oil vapors, by chlorsulphonic acid, or by any other method, the particle size distribution of the aerosol or the mist determined the screening value. So does the particle size of therapeutic aerosols similarly affect their clinical usefulness.

Colored signal smokes were aerosols of great importance. An offensive aerosol formed when certain mustard shells or bombs exploded. The burster shattered some of the toxic agent into very small droplets. Indeed, the whole subject of casualty production by means of toxic aerosols not only in the liquid state but also in the solid state was a matter of immediate concern. These few examples hardly cover the broad spectrum of important applications of aerosols in the theory and practice of chemical warfare. Other examples very close to medicine are those aerosols concerned with biological warfare.

The same theory and the same practice which was developed for the screening smoke, for the signal smoke and for the toxic aerosol, was of untold value in connection with progress in therapeutic aerosols. It was my privilege, in the fall of 1942, to be a member of the Research Branch of the Technical Division, Office of the Chief, Chemical Warfare Service. In that capacity, I was instructed to continue my earlier researches[2,4,5] on aerosol therapy by setting up a program on aerosol therapy technique,

---

Presented before the American College of Allergists, San Francisco, California, June 28 to 30, 1946.
From the Medical Services and the Division of Bacteriology Laboratories, The Mt. Sinai Hospital, New York City. Dr. Abramson is Associate Physician for Allergy.
Calcium penicillin was supplied by the Schenley Laboratories, New York City, and urea peroxide was supplied by the Buffalo Electro-Chemical Company, Buffalo, New York.
This research has been aided in part by grants from the Josiah Macy, Jr., Foundation, New York City, and the Asthma Research Foundation of Boston. It is part of a project undertaken with Dr. G. Schwartzman. Mr. B. Sklarofsky is responsible for much of the technical assistance.

with a view to therapy by antispasmodics and antibiotics within the framework of the Technical Division.*

Before discussing the details of that part of the development of aerosol therapy by the Chemical Warfare Service under my supervision,[22] definitions in the field discussed should be established. The point of view to be presented is in accord with the best usage and practice of physics and physical chemistry. It behooves us, therefore, not to disregard the practices of these fundamental sciences but, rather, to adopt them for our very own. With this in mind, let us take up the terms now current in the field of aerosol therapy and define them more explicitly.

DEFINITION OF TERMS

Aerosol and Aerosol OT.—The word "aerosol" has come to have conflicting meanings. "Aerosol OT" is a commercial wetting agent. Aerosols of this type have nothing to do directly with our present discussion. Aerosols of the type under discussion are suspensions of particles in a gas, produced by air jets, explosions, condensation of a vapor or by any other method. Although the word "aero" is from the Greek word meaning "air," its use in the word "aerosol" is much broader, since particles suspended in any gas may give rise to an aerosol. The term "sol" is generally used to denote the colloidal state. A gaseous sol or an aerosol, therefore, is a relatively stable suspension of solid or liquid particles in any gas.

Atomization.—Correctly speaking, to atomize is to reduce to atoms. It has, however, come to mean to reduce a bulk liquid to the form of a spray. Atomization procedures usually produce mists or aerosols containing most of the liquid in the form of comparatively large particles. This is the type of atomization produced by the ordinary medical atomizer. In this type of atomizer, there is no effective baffle to collide with the spray droplets. The particles are, therefore, usually larger than those generated by means of nebulizers ordinarily desirable for use in aerosol therapy of the lungs. The atomizer in common medical use forms an aerosol which is comparatively unstable because of the effect of gravity and momentum on the large particles. In aerosol therapy of the lungs, a more stable mist, with a different, smaller particle size distribution is necessary if the particles are to reach the recesses of the lungs by convection.

Nebulization.—The word "nebular" is from the Latin, meaning "cloud, mist, or vapor." This word has interlocking meanings, which may give

*The Penicillin Aerosol Project had its origin and development in meetings held in the Office of the Chief, Chemical Warfare Service. The first meeting was in Washington in August, 1942, between Col. R. W. Hufferd, chief of the Research Branch, Technical Division, Office of the Chief, Chemical Warfare Service; Dr. Frank Fremont-Smith of the Josiah Macy, Jr., Foundation; and the author, who was chief of the Physical Chemistry Section at that time. This was an interesting example of successful collaboration between the War Department and a philanthropic agency.

Two subsequent conferences, held at Edgewood Arsenal, Maryland, by the Technical Division, Chemical Warfare Service, at which the author presided, were "Aerosol Therapy of Gas Casualties," March 10, 1943, and "Aerosol Therapy of the Respiratory Tract," May 22, 1944.

rise to some confusion. The word "nebulization" should be restricted to the special type of atomization in which the large particles are removed by the introduction of a suitable baffle into the construction of

Fig. 1. The construction and distribution of the spray in the DeVilbiss No. 40 nebulizer. Note the body of the nebulizer itself acts as a baffle.

the atomizer. The construction of a nebulizer in common use, e.g., the DeVilbiss No. 40 (also No. 640), is shown in Figure 1. This nebulizer baffles out the large particles for therapeutic purposes as indicated in the figure.

Vaporization.—The word "vapor" has a very definite meaning in physics. It designates the gaseous form which a solid or a liquid takes when heated. The particles are of molecular size and are therefore about 10,000 times smaller than the particles of therapeutic aerosols now in use. Vaporization, therefore, means the production of a gas. Use of the expression "to vaporize solutions of epinephrine 1:100" or "to vaporize penicillin" is, therefore, erroneous. Neither the gaseous state of penicillin nor of epinephrine is produced. It is quite true that if water is atomized or nebulized into dry air, some or all of the water may evaporate. Indeed, the very small particles do so almost immediately, but this is not true for the pharmacologically active agents under discussion. It is,

therefore, incorrect to speak of the vaporization of these solutions. One point in favor of the term "vaporization" may be made. With nebulization therapy of the lungs, the aerosol produced is carried by inspiratory

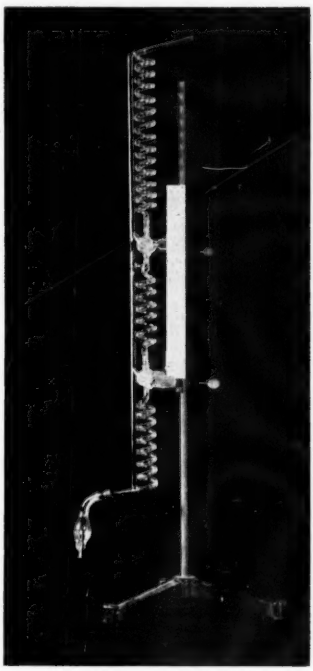

Fig. 2. A centrifugal coil attached to the nebulizer provides a method of obtaining aerosols with different particle size distributions.

action deep into the lungs by a convection process. One might say that the mass movement of the aerosol is perhaps analogous to that of a vapor. There we must stop, however, because the *movement* and *deposition* of *particles* within the lungs depends upon the *particle radius,* and, therefore, the analogy with the much smaller particles of the vapor falls down completely. This will be emphasized in the section on rebreathing. Figure 2 illustrates the centrifugal coil with which aerosols of different particle size distributions may be obtained.[5]

Aerosolization.—The term "aerosolization" apparently was introduced during the war by the group working on aerosols at Cold Spring Harbor. There is no objection to it but there is no need for its use, since the word "nebulization" covers the procedure.

HISTORICAL

The use of aerosol therapy in medicine is not new. The fumes of incense to drive away evil spirits, the burning of sulphur candles to disinfect the air, the spraying of operating rooms with germicidal materials

Fig. 3. Atomizers constructed without baffles to remove the large particles may be utilized for large particle atomization therapy of the trachea and of the bronchi. In addition, mucosagrams may be obtained with radiopaque materials. This diagram is from Farinas.

have all had evolutionary significance in our thinking. Steam inhalations and the inhalation of the smoke of asthma powder are early and still useful examples of aerosol therapy of the lungs. Indeed, when the physician recommended that his patient go to the beach to partake of the benefits of salt air, he was unwittingly suggesting the therapeutic use of the tiny salt particles in the air produced by the atomization forces of the breakers. Many pharmacologically active drugs have been employed. In the last decade, perhaps most of the emphasis has been placed upon the use of penicillin,†[8,10,16,17,24,26,27,31,35,36] sulfonamides,[11,12,25,33] epinephrine[2,4,5,15] streptomycin[13,18,19,20,21,28] and, most recently, hydrogen peroxide aerosols[1,3,6] in the topical therapy of the lungs and bronchi.

CHOICE OF EQUIPMENT

Atomizers.—Atomizers constructed without baffles, like the DeVilbiss atomizers, with adjustable tips, may be readily utilized for large particle atomization therapy of the trachea and of the bronchi. Some small particles are also produced by atomizers of this type. Quantitative studies are not available. If the finger is placed on the cut-off during inspiration with the tip directed toward the larynx (Fig. 3) it may be observed that toward the end of inspiration a fine mist is blown from the patient's mouth, even though the patient is still inspiring. This merely means

†The basic experimental communication on penicillin aerosol appeared in 1944. See reference.[10]

that the velocity of air blown in by the atomizer is greater than the velocity of inspired air and that the larger particles are baffled out by the throat. The writer has atomized as much as one ounce of 5 per cent sodium iodide solution into the trachea and bronchi in this way without irritation. This technique should be utilized for antibiotic therapy.

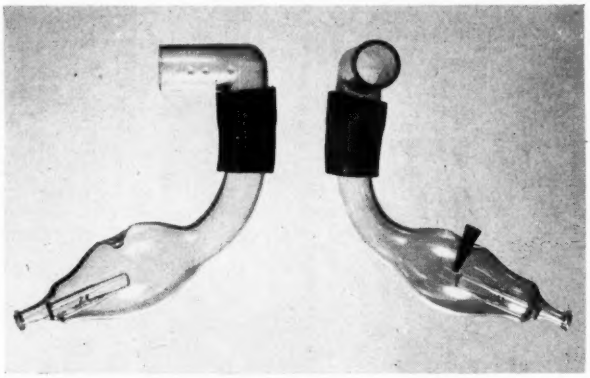

Fig. 4. For routine therapy, the DeVilbiss No. 40 nebulizer is used by the author, modified by the addition of a removable L-tube. This L-tube makes this nebulizer suitable for office use and for use with severely sick hospitalized patients (see Fig. 5). The L-tube also acts as an additional baffle to take out the small rain particles which occasionally are irritating. For short periods of therapy, the rain may be neglected but for prolonged therapy and high concentrations of penicillin the right angle of the L provides an effective baffle.

Undoubtedly, many of the smallest particles reach the recesses of the lungs. The larger particles, as will be discussed in detail shortly, coat the trachea and the larger bronchi.

A novel form of steam atomizer has been described by Prigal. This atomizer (particle size distribution not as yet reported) utilizes steam pressure instead of air pressure. According to Prigal,[29,30] his experiments indicate that steam atomization has many advantages over aerosols generated by gas pressure. Even though atomization is employed without a baffle, this method apparently leads to higher blood values for penicillin than obtained by gas pressure nebulization. However, nebulization therapy is topical therapy rather than systemic therapy. For this reason, vasoconstrictors are often added to the penicillin to *prevent* rapid absorption and high blood levels. Whether Prigal's interesting technique will provide *both* high blood levels and local therapy remains a subject for future investigations.

Nebulizers.—There are many commercial nebulizers constructed with baffles which give the particle size distribution suitable for aerosol therapy of the lungs. Most of my experience has been with the DeVilbiss No. 40 and the Vaponephrin nebulizers. The Ailene nebulizer may also be

desirable. For most general purposes, the DeVilbiss No. 40 has been modified by me by the addition of a removable L-tube†† which makes this nebulizer most suitable for use either in the office (Fig. 4), when the physician administers the mist directly to the patient, or when the

Fig. 5. This illustrates the use of the nebulizer with an L-tube attached, so that therapy may be administered to patients lying in bed without spilling the liquid and without requiring a large reservoir in the nebulizer. In the nebulizer depicted, the angle at which the nebulizer is used may be changed considerably. The L-tube gives an additional 360° zone of treatment.

patient administers the aerosol while lying in bed (Fig. 5). The use of the L-tube attached to the nebulizer by means of a rubber connection enables the patient to utilize the liquid in the nebulizer without spilling it while the head is tilted at almost any angle. Nebulizers which may spill strong epinephrine solutions into the mouth must be used with caution. The DeVilbiss No. 40 may readily be attached to a simple nasal device. This is now available as Combination No. 640. Indeed, with the use of these nasal tips, the velocity of the compressed gas being used to generate the aerosol may be raised to higher levels. In this way, therapy may be accelerated. I have already used 12 liters per minute without discomfort. Higher volume velocities will be reported subsequently.

††The L-tube was kindly made for the author by the DeVilbiss Company. It is now sold with the DeVilbiss No. 640 combination.

REBREATHING

Barach and his co-workers, as well as Segal and his collaborators,[8,31] have advocated the use of rebreathing the aerosol to conserve penicillin. With rebreathing, the patient gets aerosol delivered every other breath. This doubles the time of treatment for a given volume of liquid nebulized. In

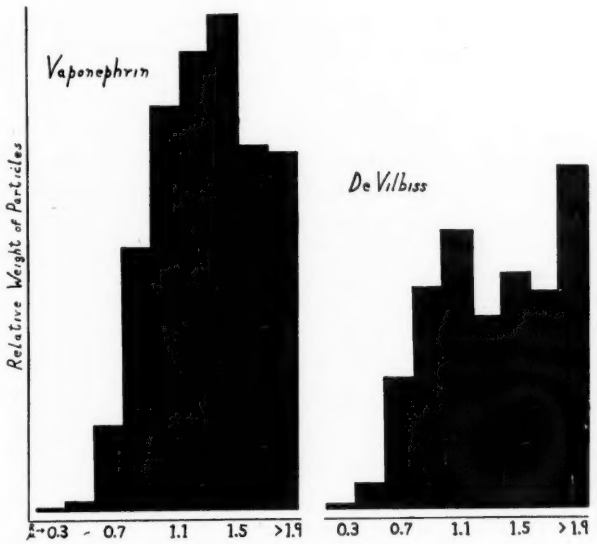

Fig. 6. The mass radius distribution of particles from two standard commercial nebulizers calculated from data of Bryson. Note that for the DeVilbiss No. 40 and the Vaponephrin nebulizers, for practical purposes, the mass of the particles is contained in those particles with radii of 0.5 micron and above. In other words, the quantity of material of the smallest particles delivered is essentially negligible. Rebreathing of these partices does not contribute in an important way to the dramatic therapeutic results achieved by aerosol therapy of the lungs.

addition to prolonging the time of treatment, study of deposition and of the particle size distribution of the aerosols generated indicates that the value of rebreathing is open to question. The deposition of particles from a heterogeneous aerosol obviously follows laws different from those determining the absorption of a homogeneous gas.

Particle Size Distribution (Radius).—Bryson's data[9] on the particle size distribution, as determined by his group under contract with the Chemical Warfare Service, of the DeVilbiss No. 40 nebulizer and the Vaponephrin nebulizer show that the therapeutically significant particles to be found in mists generated by these nebulizers are of about the same size. The particle radii extend from 0.3 micron to 2 micra, with a few particles being delivered above 2 micra. This does not include the "rain" which is apt to occur with both nebulizers because of imperfect construction. This "rain" cannot be included in the particle size distribu-

tion diagram because it is just as much of a loss as that which occurs by residual liquid clinging to the walls of the nebulizer.

Particle Size Distribution (Weight).—The weight of the particle is proportional to the cube of the radius. In aerosol therapy of the lungs, therapeutic results depend upon the dose of the drug delivered to the patient at the site of the infection. That is, the distribution of the particles of the drug in the respiratory tract will determine whether or not a suitable therapeutic result is apt to be achieved. Examination of the weight-radius-distribution curve, calculated from Bryson's data,[9] of the materials delivered by the two nebulizers under discussion discloses that in both of these nebulizers, for practical purposes, the mass of the particles is contained in those particles with radii of 0.5 micron and above (Fig. 6). In other words, the quantity of material in the very smallest particles delivered by the nebulizer is essentially negligible and is probably connected only in a minor fashion with the dramatic therapeutic results achieved by aerosol therapy.

Distribution of Particles in the Lungs.—According to Findeisen,[14] particles of 3 micra and above are taken out completely by the trachea, the bronchi, the bronchioles and the alveolar ducts. Particles of 1 micron radius and above are taken out by the lungs to the extent of 97 per cent, with only 3 per cent recovered on expiration. As the radius of the particle gets smaller, particles of 0.3 micron in radius are absorbed to the extent of only 35 per cent, with 65 per cent recovery on expiration. These conclusions of Findeisen are confirmed by the experimental work of Van Wigh and Patterson[34] who showed that solid particulate material of 0.6 micron in radius was removed to the extent of 63 per cent while particles from 0.6 micron in radius to 2 micra in radius were removed from 63 per cent to 96 per cent. Particles less than 0.4 micron in radius were retained only to the extent of about 30 per cent. All of these data support the view that rebreathing equipment is an unnecessary addition for routine aerosol therapy. With a suitable nebulizer and with the proper technique of making certain that the aerosol is provided for the initial phase of inspiration, excellent therapeutic results have been obtained without rebreathing. This is borne out by the extensive experiences of Olsen at the Mayo Clinic and by my own. All that is required for successful aerosol therapy is a suitable nebulizer and a piece of rubber tubing with a small hole, about 5 mm. in diameter, for a cut-off about one inch from the nebulizer. No Y-tube is required. The L-attachment and the nasal tip are optional but convenient.

Barach, Garwaithe and Rule[7] have applied the centrifugal baffle-nebulizer combination described by Abramson and Demerec[5] to remove large particles which may irritate the patient's tongue and throat. It is, however, unnecessary to use this device of Abramson and Demerec because, for

practical purposes, the L-attachment just described removes substantially all of the large particles quite effectively. It is well known that forcing an aerosol to take a right angle turn takes out most of the large particles. For this reason, the L-tube is recommended for routine use.

TECHNIQUE OF STABILIZATION OF PARTICLE SIZE OF AEROSOLS

The importance of particle size distribution has been mentioned. It will now be emphasized. In order to have the lungs retain a reasonable percentage of particles inspired, it is necessary that the particles remain above a given critical radius. This radius, judging by the data that is available at present, is approximately 0.5 micron. With commercially available nebulizers, such as the DeVilbiss No. 40 and the Vaponephrin nebulizers, it is very striking to see the phenomenon which occurs when water or physiological saline solution is nebulized. The very fine mist of droplets which is formed disappears quite rapidly because the small size of the droplets leads to an evaporation rate far above the normal. The life period of a water droplet 0.5 micron in radius, under ordinary conditions of humidity, is only a fraction of a second. The salt solution droplet evaporates until the increase of salt concentration reduces the vapor pressure sufficiently to prevent evaporation. This phenomenon is of importance in the nebulization of 1:100 epinephrin salt solutions for the relief of bronchial obstruction. Droplets of solutions which do not contain materials to lower the vapor pressure diminish rapidly in size after leaving the nebulizer, and absorption is variable because of the unpredictable particle size distribution of smaller particles. Examination of the mathematical theory of nebulization discloses that there are two essential factors which control the particle size and persistence of mists of aerosols.[2,4,5] These variables are (1) the vapor pressure of the droplets, and (2) the surface tension of the droplets. Experiment has shown that substances which lower the vapor pressure of the droplet sufficiently produce a more stable mist. For nebulization therapy of the lungs, therefore, it is important to add a substance which stabilizes the particle size distribution. For practical purposes, glycerol is suitable. Indeed, the army has adopted a solution of 1 per cent epinephrine salt containing 25 per cent of glycerol (Stock No. 1175320, July 16, 1945). In addition to stabilizing the mist, glycerol reduces irritation and may retard absorption.

Substances other than glycerol may also be used, e.g., urea for its bacteriostatic qualities, as well as sugar and salts. All of these act to stabilize the mist by lowering the droplet vapor pressure.

When strong penicillin solutions are nebulized, it is unnecessary to add glycerol because the penicillin itself apparently acts to stabilize the particle size distribution. The behavior of streptomycin in strong solutions is similar to penicillin. With hydrogen peroxide, 10 per cent of glycerol is sufficient.

Lowering the surface tension may produce a different particle size distribution but the stability also may *decrease* if smaller particles are formed as frequently occurs, e.g., with alcohol. A minute quantity of a detergent (e.g., Aerosol OT) does *not* stabilize particle size.

CLINICAL APPLICATION OF AEROSOL THERAPY

This discussion will be restricted to drugs and antibiotics which are either of definite practical value or are recent experimental techniques which may eventually become of importance. For this reason, epinephrine, penicillin, streptomycin, sulfonamide and hydrogen peroxide aerosols will be treated. Combinations of these are also of importance since the possibility of synergism exists.

Epinephrine.—Epinephrine aerosols have been used in very dilute solution effectively by direct atomization into the trachea or in prolonged therapy with nebulizers. Since some small particles are always produced by most atomizers, some epinephrine reached various parts of the respiratory tract. The introduction in 1935 of higher concentrations of epinephrine up to 1:100 epinephrine salt solutions, and the use of nebulizers with proper particle size distribution, led to more effective aerosol therapy by epinephrine.[15]

Epinephrine salt solutions should preferably be between pH 4 and 5 (the author uses the phosphate) and should contain glycerol or some other substance to stabilize the particle size distribution of the mist.

Failures with solutions of this type are often due to:

1. Insufficient solution being nebulized.
2. Poorly constructed nebulizer.
3. Insufficient glycerol or other stabilizing substance.
4. An excessive amount of secretion in the bronchial tree, preventing access of the aerosol to the points required.

The patient should be instructed to use the aerosol, if possible, to prevent the attack. Excellent results with epinephrine aerosol therapy justify the statement that in most cases inhalation can replace injections.

Penicillin.—The feasibility of bringing biologically active materials (other than epinephrine) like enzymes (lysozyme) and endocrines (e.g., insulin) into the lungs by means of the aerosol technique was emphasized by the writer[2,4,5] in 1940, leading directly to the further development of the fundamental properties of aerosols and to the penicillin aerosol therapy project of the Chemical Warfare Service during the war.[22]

Penicillin aerosols for the therapy of the lungs were initiated and organized for the Technical Division, Chemical Warfare Service by the writer, in collaboration with the Josiah Macy, Jr., Foundation. It was the responsibility of the chief of the Chemical Warfare Service to con-

sider not only casualties due to chemicals, but also to those agents classified under the heading of bacteriological warfare.† It can readily be understood, therefore, that in the fall of 1942 it appeared important to initiate and develop for topical use in the lungs aerosols of antibiotics and chemotherapeutic agents, for the treatment of both primary and secondary infections arising from casualties due to the many types of chemical warfare agents.

Among the projects was that of a group of investigators at the Long Island Biological Laboratory, Cold Spring Harbor, New York, under contract to the Technical Division, Chemical Warfare Service, charged with making fundamental studies on aerosols with a view to perfecting equipment for aerosol therapy of the lungs in the field and to survey both chemical and antibiotic means of treating lung infections. Bryson, Sansome and Laskin,[10] working under contract with the Technical Division, made the following points in their report on the first published use of penicillin aerosols in animals and in man:

1. Penicillin solution was not altered to any extent by the gas flow incidental to nebulization.
2. The penicillin formed an aerosol that was readily recovered with no sensible loss of activity.
3. Penicillin aerosols readily penetrated the lungs of animals and man.
4. Penicillin could be recovered from the lung tissues of animals treated with penicillin aerosols.
5. Penicillin aerosols diffused from the respiratory tract into the blood stream.
6. Recovery of penicillin from the urine of human volunteers was readily accomplished.
7. As much as 250,000 units of penicillin per c.c. could be nebulized and inhaled without lung injury.

This work was reported to the Technical Division early in the winter of 1944. Because of its obvious importance, a meeting of interested agencies took place at Edgewood Arsenal in the spring of 1944 and collaboration was established with clinical groups. Barach of Columbia University co-operated with the Technical Division and with the Cold Spring Harbor group in studies of penicillin aerosol. Barach and his co-workers confirmed the work of Bryson, Sansome and Laskin and, in addition, made the following additional contributions:[8]

1. The administration of penicillin aerosol was a practical clinical procedure.
2. Most Gram-positive organisms were consistently absent from the sputum during penicillin aerosol therapy.

†The June 15, 1946, issue of *Colliers* has an authentic survey of the importance of biological and bacteriological warfare as a technique of war.

3. Certain types of nontuberculous suppuration were improved by penicillin aerosol therapy.

In addition, it was shown that rates were protected against intraperitoneal injection of hemolytic streptococci by a single massive inhalation of penicillin aerosol. Subsequent animal experiments reported by Wilson[36] and her co-workers also showed that experimental bacterial pneumonia can also be cured by penicillin aerosol.

The literature on penicillin aerosol has grown rather rapidly. Different dosages have been employed. Thus Olsen[27] started with 5,000 units for ten hours per day, ten minutes on and ten minutes off. Others have used higher concentrations with fewer treatments. I believe that position intermediate between the high and low concentrations is desirable, depending upon the type and distribution of infection. This intermediate dosage should depend upon the type of pathologic condition present in the lung. Certainly with diffuse suppurating large bronchiectatic lesions, the difficulty of reaching all parts of the lungs must be considered. For this type, the procedure of Olsen may be superior, for with prolonged administration the probability of reaching all parts of the lungs increases. If the injury is less, such as in asthma complicated by infectious bronchitis, higher dosages at longer intervals may be more suitable. Olsen used a non-rebreathing technique for the pre-operative treatment of surgical bronchiectasis and for the inhalation therapy of nonsurgical bronchiectasis. Most of the surgical cases were benefited by the pre-operative use of penicillin. There was also general improvement in the cases of nonsurgical bronchiectasis with dimunition of sputum and change in the flora of the respiratory tract. Segal and Ryder, using a different technique, that is, the rebreathing equipment of Barach, also reported favorable results. In addition, Segal and Ryder[31] showed that seven patients with pneumococcus pneumonias were cured when penicillin aerosol was administered over a period of from three to seven days. The sputum became negative by the third day of treatment. In my own work, using the DeVilbiss No. 40 and the Vaponephrin nebulizers without rebreathing, the work of Olsen has been confirmed in the therapy of both surgical and nonsurgical bronchiectasis, as well as infection complicating bronchial asthma. Time is too brief to discuss all of the clinical reports which have appeared. It is pertinent to mention certain of the clinical difficulties which should be borne in mind when penicillin aerosols are employed. Occurrence of hives following penicillin aerosol therapy is well known. In addition, a red tongue and sore throat may occur, especially with higher dosages and incorrect technique. However, of some importance is the possibility of severe allergic reactions. Dundon[6] observed a patient with tuberculosis, under treatment with combined penicillin and hydrogen peroxide aerosol therapy, who developed edema of the lungs while receiving penicillin. The first sign in this patient that she was allergic to penicillin was indicated by swelling of the lips.

Hurst[23] reports frequent occurrence of tightness in the chest with wheezing in patients treated with sodium penicillin. Apparently, this reaction occurs less often with calcium penicillin, which is the preferred preparation at present. Mutch and Rewell[26] have shown that penicillin aerosol is rapidly absorbed through the respiratory mucous membrane. They believe that with their technique about 75 per cent of the material is lost. Of some interest is their statement that after one-half hour's inhalation of penicillin aerosol, from a solution of calcium penicillin containing 80,000 units of penicillin per c.c., more than one unit per c.c. of blood was obtained. It will be of interest to repeat their experiments.

Although this communication deals with penicillin aerosol therapy, the treatment of the patient should not be restricted to aerosol therapy alone. In certain instances, it may be desirable to give penicillin by injection, by large particle atomization, or to install penicillin directly into the lungs by means of a catheter or the bronchoscope so that appreciable quantities of penicillin may be deposited locally in walled off areas. Siltzbach[32] has reported successful results by direct installations. In addition, it is of importance in cases complicated by asthma to use epinephrine 1:100 as an aerosol to relieve bronchial obstruction.

Streptomycin.—Olsen[28] has studied a group of patients with streptomycin aerosol in cases that did not show suitable reduction in the volume of the sputum. Smears and cultures revealed that the penicillin had been effective in removing Gram-positive organisms but numerous Gram-negative organisms remained. In these cases, the organisms were found to be streptomycin sensitive *in vitro.* A total of 500,000 units of streptomycin, dissolved in 20 c.c. of physiological saline were nebulized each day. In certain instances, combined penicillin and streptomycin therapy were used. In each of the nine cases in which streptomycin aerosol was employed, the Gram-negative bacteria disappeared rapidly from the pulmonary secretions, and the volume of sputum was immediately reduced. Although none of the patients became entirely sputum free, the remaining sputum lost its purulent character.

Sulfonamides.—The emphasis which might have been placed on sulfonamides has been overshadowed by the introduction of antibiotics. Castex and his co-workers have demonstrated that a 5 per cent solution of sulfanilamide may be used in the therapy of pulmonary suppuration. Micro crystals of sulfathiazole, as well as nebulized sulfathiazole solutions, have also been used. Therapeutic claims await confirmation.

The work of Mutch[25] merits special comment. Mutch has made a systematic survey of sulfonamide absorption and excretion with three different types of nebulization equipment delivering the mist: (1) directly to the mouth, (2) through oro-nasal face piece, and (3) through a nose piece, the mouth being used as an expiratory valve. The greatest

absorption and excretion occurred with the third method as might be anticipated. According to Mutch, approximately 10 per cent of the sulfonamide solution, which he used with his nebulization system, reaches the blood stream. According to Mutch, steady increase of the urinary output of sulfonamides occurs when the opportunity for turbulence complications in the apparatus and in the respiratory tract is diminished. However, increased absorption in the nose may also account for Mutch's results. On the other hand, with certain types of patients, the nasal route for aerosol therapy of the lungs may be preferred.

Hydrogen Peroxide.—Hydrogen peroxide aerosols have been used alternating with penicillin for the treatment of both tuberculous and nontuberculous pulmonary suppuration.

(1) Nontuberculous suppurative disease.[1,3] Hydrogen peroxide solution, as urea peroxide, may be readily nebulized without loss of stability. Hydrogen peroxide itself may also be used. Germicidal concentrations have been administered to both animals and man without appreciable irritation and with no demonstrable lung injury. A limited number of cases of asthma, asthma complicated by infectious bronchitis, bronchiectasis with and without lung abscess, as well as tuberculosis, have been treated by combining penicillin therapy with hydrogen peroxide aerosol therapy. This technique provides a method of approach to the destruction of both Gram-positive and Gram-negative organisms with readily available antibiotic material. In most of the cases studied thus far, the penicillin has been administrered from two to four days, followed by 3 per cent urea peroxide plus 10 per cent glycerol dissolved in physiological saline, for two days. Slight irritation of the throat may be observed at the end of the second day but this condition may be diminished by having the patient gargle in the same way as is done for penicillin irritation. One patient has taken 3 per cent urea peroxide for two weeks, followed by 5 per cent urea peroxide for four days, without irritation or injury. The preliminary results of nontuberculous lung infections indicate that this combined antibiotic therapy may be an important technique in handling chronic suppurative pulmonary disease. Hydrogen peroxide alone is not as effective as when used alternatingly with penicillin as described.

In one experiment, hydrogen peroxide aerosol was administered for a period of two weeks. The last five days of the period, a concentration as high as 1.6 per cent was used. Although the patient claimed that his cough had improved and the sputum had become more liquid, the bacteriological flora remained without significant change. Study of the sputum revealed that there was a large amount of catalase present. For this reason, an intensive search is being made for a suitable anticatalase which can be added to the hydrogen peroxide solution to be nebulized to retard the effect of this enzyme on the decomposition of the peroxide.

In this way, it is hoped that the bactericidal properties of the peroxide will be markedly increased. An anticatalase, e.g. Vitamin C, could also be administered before the peroxide. Experiments with ascorbic acid as well as with sodium ascorbate are now in progress. Aerosols of sodium ascorbate as concentrated as 10 per cent may be inhaled. Ascorbic acid itself is irritating. The rate of destruction of the sodium ascorbate produced by nebulization with oxygen and air is under active investigation by the author.

(2) Tuberculosis. Two typical chronic advanced cases of pulmonary tuberculosis without material clinical symptoms except paroxysmal cough and positive sputum have been treated.[6] In one case, laryngeal pain was relieved by penicillin aerosol shortly after the beginning of therapy. In the course of a month of combined penicillin and hydrogen peroxide therapy, the cough was less forceful and not distressing to the patient. The purulent character of the sputum decreased, with a decrease in viscous quality. The tubercle bacillus remained on smear and culture, together with an unidentified Gram-negative bacillus. In the second case, the improvement of the patient was the same, with the tubercle bacillus persisting in the sputum and on smear and culture. The time in which this new type of therapy of tuberculosis has been used is too short to draw any conclusions other than that it appears to be effective in relieving certain symptoms such as cough and laryngeal pain in the type of patients studied. It will most probably be of value at least in the following:

(a) Adjuvant therapy to reduce or eliminate secondary infections in advanced tuberculosis.

(b) Prophylactically in the prevention of secondary infection in early tuberculosis.

SUMMARY

1. Penicillin aerosol therapy of the lungs was initiated and organized for the Technical Division, Chemical Warfare Service, by the writer in collaboration with the Macy Foundation and other agencies.

2. The relationship of aerosols to general problems in the Chemical Warfare Service is discussed.

3. Definitions of aerosol, atomization, nebulization, vaporization and aerosolization are considered.

4. Large particle atomization and small particle nebulization are described in detail.

5. It is shown on the basis of the study of particle size distribution by radius and by weight that rebreathing is inefficient and not desirable.

6. Simple apparatus is described which is inexpensive and which can be used for all routine antibiotic aerosol therapy of the lungs.

7. The clinical application of aerosol therapy is considered from the point of view of the use of epinephrine, penicillin, streptomycin, sulfonamide and hydrogen peroxide aerosols. Preliminary data are dis-

cussed on the use of antibiotic and hydrogen peroxide aerosols in the treatment of secondary infection in pulmonary tuberculosis.

8. The difficulties of using hydrogen peroxide are stressed because of the presence of catalase in the sputum.

9. It is believed that in the presence of a suitable anticatalase, hydrogen peroxide aerosol will become one of the most efficient antibiotic substances for pulmonary therapy.

REFERENCES

1. Abramson, H. A.: Aerosol therapy of the lungs and bronchi with special reference to penicillin and hydrogen peroxide. Bull. New England M. Center, 8:97, 1946.
2. Abramson, H. A.: A stable hydrogen peroxide aerosol. Science, 96:238, 1942.
3. Abramson, H. A.: Combined hydrogen peroxide and penicillin aerosol therapy of the lungs. Ann. Allergy, 4:199, 1946.
4. Abramson, H. A.: Improved inhalation therapy of asthma. Arch. Phys. Therapy, 21:612, 1940.
5. Abramson, H. A., and Demerec, M.: Method for experimental control of particle size of therapeutic aerosols. J. Allergy, 16:184, 1945. (Classified as "confidential" after submission to the Chemical Warfare Service in 1942).
6. Abramson, H. A., Kolb, E. P., et al.: Addendum to reference[3] on effect of combined penicillin and hydrogen peroxide aerosol therapy on the primary and secondary infection in pulmonary tuberculosis. Ann. Allergy, 4:199, 1946.
7. Barach, A. L., Garwaithe, B., and Rule, C.: Penicillin aerosol in bronchiopulmonary and sinus infections. New York State J. Med., 46:1703, 1946.
8. Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T., and Soroka, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectasis and lung abscess: preliminary report. Ann. Int. Med., 22:485, 1945.
9. Bryson, V.: Personal communication.
10. Bryson, V., Sansome, E., and Laskin, S.: Aerosolization of penicillin solution. Science, 100:33, 1944.
11. Castex, M. R., Capedehourat, E. L., and Pedace, E. A.: Nuevo tratamiento de las supuraciones bronchopulmonares: accion curativa de un preparado sulfamidico nebulizada. Rev. Asoc. méd. argent., 55:85, 1941.
12. Chambers, L. A., Harris, T. N., Schumann, F., and Ferguson, L. K.: Use of microcrystals of sulfathiazole in surgery. JAMA, 119:327, 1942.
13. Figi, F. A., Hinshaw, H. C., and Feldman, W. H.: Treatment of tuberculosis of the larynx with streptomycin. Proc. Staff Meet., Mayo Clin., 21:127, 1946.
14. Findeisen, W.: Uber das Absetzen kleiner, in der Luft suspendierter Teilchen in der menschlichen Lunger bei der Atmung. Arch. f.d. ges Physiol. (Pflüger's), 236:367, 1935.
15. Graeser, J. B., and Rowe, A. H.: Inhalation of epinephrine for relief of asthma symptoms. J. Allergy, 6:415, 1935.
16. Hagens, E. W., Karp, M., and Farmer, C. J.: Inhalation method for penicillin therapy: preliminary report. Arch. Otolaryn., 41:333, 1945.
17. Hanks, R. J.: Nebulized penicillin in treatment of respiratory infection. Texas State J. Med., 41:253, 1945.
18. Harrell, W. E., and Nichols, D. R.: The clinical use of streptomycin. Proc. Staff Meet., Mayo Clin., 20:449, 1945.
19. Heilman, D. H., Heilman, F. R., and Harrell, W. E.: Streptomycin absorption, diffusion, excretion and Toxicity. Proc. Stag Meet., Mayo Clin., 20:408, 1945.
20. Heilman, D. H., Heilman, F. R., Hinshaw, H. C., Nichols, D. R., and Harrell, W. E.: Streptomycin: absorption, diffusion, excretion and toxicity. Am. J. Med. Sci., 210:596, 1945.
21. Hinshaw, H. C., and Feldman, W. H.: Streptomycin: A summary of clinical and experimental observations. J. Pediat., 28:269, 1946.
22. Hufferd, R. W.: Penicillin aerosol: contribution of the Chemical Warfare Service to medicine. Science (in press).
23. Hurst, A.: Penicillin nebulization in bronchopulmonary disease. Rocky Mountain M. J., 43:219, (March) 1946.

(Continued on Page 475)

CONTACT TESTING OF THE BUCCAL MUCOUS MEMBRANE WITH SPECIAL REFERENCE TO PENICILLIN

LEON GOLDMAN, M.D., and JOSEPH FARRINGTON, M.D.
Cincinnati, Ohio

IN a previous report[5] the techniques for contact-testing of the buccal mucosa were given. More work is needed before such testing can become standardized or, at least, as well standardized as the cutaneous patch test. Some of the more obvious difficulties of the buccal mucosa contact-test continue to be the determination of the most desirable, and yet practical, time interval of contact and also the concentration of the contactant. Irritant mechanical reactions from the testing materials, such as the rubber cups and the like, must be differentiated from the more diffuse sensitivity reaction of the contactant. The differentiation from the localized primary irritant reaction is more difficult, and control testing to the cup alone is recommended. Such irritant mechanical reactions may occur with prolonged contact periods and in patients with dentures to which the testing cups are fastened. Moreover, the question of the detection of primary irritation of the buccal mucosa is also of considerable interest, especially in relation to dentrifices and the like.

It seemed advisable to study penicillin in relation to sensitization of the buccal mucosa. This should be important not only because of the role of penicillin in modern therapeutics but also because of the frequency of local contacts in the mouth with penicillin through topical therapies, the use of oral penicillin therapy and aerosol therapy, and the excretion of penicillin in the saliva.

In an attempt to determine concentrations of primary irritation, twenty patients were tested with approximately 0.5 mg. of crystalline sodium penicillin (approximately 1,500 units of penicillin per milligram) sprinkled on a cotton plug in contact with buccal surface of the upper lip. Some of these patients had had previous penicillin therapies or previous or simultaneous penicillin cutaneous patch-testing studies as detailed in our report[4] on eczematous hypersensitivity from penicillin. The contact period was fifteen minutes, and no reactions were found. Five patients were tested by means of the cup technique, with approximately the same quantities of penicillin, for three-hour contact periods with equally negative results. An attempt was made in this latter series to determine whether any penicillin remained in the testing pad. The pads were removed from the cups and soaked in saline. Small amounts of penicillin were found in the pads from two patients, while in the third patient the pad came off and saline irrigation of the cup revealed no penicillin at the end of the test period. Also at this time no penicillin was detected in the saliva of the

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati and the Laboratory of Anti-Biotics of the Cincinnati General Hospital, Joseph Tamura, PhD., Director.

Read at the meeting of the American College of Allergists, San Francisco, California, June 28 to 30, 1946.

patients. In five patients, twenty-four-hour testing techniques with the rubber cup method were done with crystalline penicillin, and no positive reactions were found. In several instances, the cotton pads were soaked in saline and the saline solution tested for penicillin, and small amounts of penicillin (0.15 units) were found in the pad from one patient. Additional work is continuing in these control series with quantitative studies of the concentrations of penicillin remaining on the pads and also of the concentration of the penicillin in the saliva. From this small control series it was evident that, at least for the brief periods of contact, crystalline penicillin caused no reaction on contact with the buccal mucous membrane. Only three patients of this control series were available two weeks later for repeat contact-testing for a fifteen-minute period, and these were negative. An effort will be made to acquire a large enough series of this type. In five patients with recurrent aphthous stomatitis, thirty-minute contact tests, with a stable calcium penicillin ointment of 500 units per gram, were negative. Dentists are using crystalline penicillin to pack tooth cavities and have reported, to date, no irritation or apparent interference with healing. Previously, dentists and dental surgeons had used penicillin mixtures containing much lower concentrations of penicillin.

In actual clinical practice, proved penicillin stomatitis must be rare when one considers the frequency of the use of penicillin. Dryness, burning, et cetera, have been described following the use of troches, but these may be due as much to the vehicles as anything else. Wright and Rule[7] have reported papules of the soft palate, tongue and buccal mucosa, discoloration of the tongue, sore throat and even ulcers on the anterior tonsillar pillars as reactions to the use of penicillin lozenges in the treatment of oral lesions. As far as can be determined, no detailed testing has been done to evaluate such symptoms. Burmeiester[1] has described edema of the uvula, and in another case, diffuse redness and swelling of the mouth following the use of penicillin troches. No mucous membrane tests were done. With the present use of topical penicillin-sulfa mixtures by the dentists and dental surgeons, extensive testing will have to be done in rare cases of stomatitis or even of dermatitis following such therapies. Urbaitis[6] reported, in himself, dermatitis of the face, cheilitis and even vesicles on the tongue following nebulization of a saline penicillin mixture for the therapy of a laryngitis. His skin test to penicillin was "mildly positive." No mucous membrane tests were done. Aerosol penicillin therapy has produced dermatitis of the face but no stomatitis has been reported as yet. Only two examples of penicillin stomatitis were found in our series. In one instance, a patient under local therapy with calcium penicillin ointment, 500 units per gram, for an ulcerative gingivitis on a fuso-spirillar basis, developed a diffuse redness, swelling and burning of the buccal mucosa after three days of local therapy. The gingivitis improved under the combination of local therapy plus polyvitamin mixtures, and the diffuse stomatitis subsided shortly after the penicillin was

discontinued. Buccal mucosa penicillin tests, both ointment and crystalline, with thirty minutes of contact were positive. Cutaneous patch testing on the upper arm to crystalline penicillin, two commercial penicillin ointments, "penicillin impurity mixture," and a penicillin-penicillinase mixture were all positive. Such wide range of reactions to penicillin combinations had been noted before in our work with eczematous reactions to penicillin. No attempt was made to induce a penicillin dermatitis in this patient. The second patient with penicillin stomatitis was a seventy-eight-year-old white man who developed a severe dermatitis exfoliativa from parenteral penicillin therapy. This patient with his detailed cutaneous tests has been reported by Farrington and Tamura.[2] During the acute phase of his dermatitis exfoliativa, he developed numerous areas of vesiculation and erosion in his mouth. After recovery, twenty-four hour contact-testing of the buccal mucosa was positive to crystalline penicillin. His positive cutaneous tests included patch tests and intradermals, both urticarial and tuberculin types to various penicillin combinations.

An effort was made also to study the buccal mucosa reactions in patients developing an eczematous hypersensitivity to penicillin. No patient of this group of sixteen patients, thirteen of whom have been reported previously,[4] had any clinical evidence of stomatitis. However, cheilitis venenata was present in some instances and will be mentioned later. Four patients of the eczematous hypersensitivity group, all with facial dermatitis, were tested to penicillin and all revealed positive tests. One of these patients with an associated cheilitis venenata had a negative buccal mucosa test, after only five minutes of contact, to the ointment which had caused the dermatitis and cheilitis. However, simultaneous testing for the same time interval with crystalline penicillin, type G predominantly, gave a positive reaction. Another patient of this eczematous dermatitis group had been "artificially" sensitized to penicillin by repeated rubbings of penicillin ointment on the clear skin of his face. This patient was an elderly white male with psoriasis, but with no psoriasis of the face. He had a previous eczematous hypersensitivity to coal tar. Pre-rubbing penicillin patch tests were negative, post-rubbing patch tests were positive, and mucous membrane test was likewise positive. The penicillin dermatitis which this patient developed was a typical vesicular form. All four patients with positive buccal mucosa contact tests had also positive cutaneous patch tests. Two additional patients with a cheilitis venenata, one clinically from penicillin ointment contact and one possibly from penicillin, had negative penicillin buccal mucosa tests. The former patient had a definite flare-up reaction with direct lip test; the other patient refused such a test.[3]

One patient with a maculopapular penicillin eruption, especially marked on the trunk, was tested, and his buccal mucosa cutaneous patch and intradermal tests to penicillin were all positive. His eruption had been

produced by parenteral penicillin. An additional patient, a physician, with a history of repeated espisodes of vesicular dermatitis of the hands (an epidermophytide?) developed an endogenous penicillin dermatitis of the hands and feet following parenteral therapy for a severe pharyngitis. Prior to the intramuscular penicillin he had tried penicillin troches without relief. After his dermatitis cleared, his buccal mucosa test to crystalline penicillin was positive. Cutaneous patch and intradermal tests were also positive. The intradermal trichophytin test was positive but the intradermal streptomycin test was negative.

Therefore, patients with eczematous hypersensitivity, and even possibly other types of penicillin sensitivity, may have potential eczematous hypersensitivity of the buccal mucosa also. This relationship has been shown before with other substances such as nickel. For the penicillin studies, much work must be done to evaluate this potential hypersensitivity in practical terms as regards the local use of penicillin. This would include relatively transient use, such as oral medications, aerosol therapies, or the more prolonged time contacts as in topical therapies, et cetera.

CONCLUSIONS

With the unstandardized buccal mucosa contact-testing techniques now available, crystalline penicillins were found not to cause reactions in a small series of control patients with fifteen-minute contact (the largest group), and also in some with thirty-minute, three-hour, and twenty-four-hour contact periods. Two cases of proved penicillin stomatitis are reported. One patient developed his stomatitis from topical penicillin therapy of an ulcerative gingivitis, the other patient had his stomatitis as part of the picture of a severe dermatitis exfoliativa from parenteral penicillin. A small series of four patients with eczematous contact hypersensitivity to penicillin were found to exhibit also potential mucous membrane hypersensitivity as demonstrated by contact-testing of the buccal mucous membrane. One other patient with a generalized maculopapular endogenous dermatitis from penicillin, and a second patient with endogenous penicillin dermatitis of the hands and feet also showed positive contact tests to penicillin on the buccal mucosa. This potential mucous membrane hypersensitivity to penicillin has not, as yet, been evaluated in practical terms as regards future clinical contacts with penicillin in the mouth. Because of the lack of the knowledge of the true mechanisms of reactions from penicillin, detailed testing should be done in all types of such reactions. In spite of the frequency of oral penicillin therapy, topical penicillin therapy in the mouth, aerosol therapy and the like proved stomatitis from penicillin is as yet an uncommon reaction.

REFERENCES

1. Burmeister, C. H.: Personal communications to the authors.
2. Farrington, Joseph, and Tamuro, Joseph: Cutaneous testing in a case of exfoliative dermatitis caused by penicillin. (In press.)

(Continued on Page 504)

Department of Clinical Pathology and Laboratory Procedures

BONE AGE STUDIES IN CHILDREN TO ESTABLISH DIAGNOSIS OF HYPOTHYROIDISM

L. O. DUTTON, M.D., F.A.C.A.
El Paso, Texas

THE implication of the literature is that better developed and more superior children are more apt to exhibit allergic conditions than are the less well developed. However, in my experience, there are a sufficient number of exceptions to this rule to warrant being on guard against overlooking those exceptions and thus denying them the help that can be given. The allergist frequently finds himself in the position of being the arbiter of his patients' general problems. Successive episodes of various allergic manifestations from infancy to adulthood place the child under his observation for long periods during that time when abnormalities of physiology are capable of exerting the most profound effect upon the entire future health of the individual.

Not the least of such possibilities is an aberrance of the endocrine system, and perhaps the most common of these is hypothyroidism.

I do not wish to argue the relationship between endocrine disorders and allergy, but it is well established that a significant number of children (15 to 18 per cent) do exhibit hypothyroidism. It seems pertinent, therefore, to remain aware of this possibility and to utilize the best means of establishing such a diagnosis.

Without discussion of the clinical picture of this condition, it can be said that numerous children, perhaps a great majority, who actually have a deficient thyroid, do not exhibit an easily recognizable clinical pattern. Certainly the classical textbook picture of profound hypothyroidism is only rarely seen.

Diagnostic aids in such a situation become important and mandatory.

One's first thought in this regard is the basal metabolic rate determination. This test, however, is utterly useless when performed on children. In a recent summary, Wolman[2] effectively presents the present day opinion of the workers in this field, with the conclusion that the BMR cannot be utilized to support or rule out the diagnosis of hypothyroidism in children. That this fact is not universally appreciated is attested by the continued requests to laboratories to do this test on children.

By far the simplest, least expensive, and least time consuming test for hypothyroidism in children is a determination of the bone age by x-ray.

It is also the most reliable evidence of the existence of this condition. This has long been known. Clark[1] presents an excellent article giving details of the technique and interpretation. Yet roentgenologists tell me that very few such studies are requested of them. The summary of Clark is so to the point that I quote:

"There are two possible ways of investigating the metabolism of individuals in the pre-adult age group: the respiratory method and roentgen examination of the epiphyses. From the age of one year until the onset of puberty, roentgen examination has a definite advantage in availability, economy and accuracy. From the onset of adolescence until adult life is reached, basal metabolic studies are more informative in acute endocrinopathies, while roentgen examination is of more value in chronic endocrine disorders. The practical use of roentgen examination of the epiphyses is discussed and the possible sources of error described.

"The hormones chiefly concerned in the control of osseous development and growth are thyroid hormone, sex hormone, growth hormone and the gonadotropic and thyrotropic fractions of the anterior lobe of the hypophysis. Prolonged disturbances in the elaboration of these hormones result in recognizable disturbances of epiphyseal growth and development."

In addition to bone age studies, blood cholesterol determinations may reveal hypercholesterolemia as a confirmatory diagnostic aid.

This brief discussion seeks to make two points only.

1. Remain alert as to the possibility of hypothyroidism in children.
2. Utilize the most reliable and universally available means, namely, bone age studies, to establish its very probable diagnosis.

REFERENCES

1. Clark, Daniel M.: The practical value of roentgenography of the epiphyses in the diagnosis of pre-adult endocrine disorders. Am. J. Roentgenol., 40:752, (June) 1936.
2. Wolman, Irving J.: Basal metabolism in childhood. Am. J. M. Sc., 211:733, (June) 1936.

Differential Diagnosis of Bronchial Asthma

(Continued from Page 424)

35. Smith, E. E.: Ayerza's disease. J. Pediat., 14:602, 1939.
36. Sodeman, W. A.: Some problems in the differential diagnosis of bronchial asthma. Am. J. M. Sc., 210:114, 1945.
37. Swineford, O., Jr., and Magruder, R. G.: Asthma in heart disease. South. M. J., 30:829, 1937.
38. Toomey, J. A., and Petersilge, C. L.: Dust bronchitis. J. Pediat., 25:25, 1944.
39. Unger, L.: Bronchial Asthma. P. 240. Springfield, Illinois: Charles C. Thomas, 1945.
40. Unger, L.: Bronchial Asthma. P. 234. Springfield, Illinois: Charles C. Thomas, 1945.
41. Waldbott, G. L.: Pathologic changes in asthmatic infants. Am. J. Dis. Child., 49:1531, 1935.
42. Young, M., and Turnbull, H. M.: An analysis of the data collected by the Status Lymphaticus Investigation Committee. J. Path. & Bact., 34:213, 1931.

Editorial

The opinions expressed by the writers of editorials in the ANNALS *are individual and do not necessarily represent the group opinion of the Board or of the College.*

PENICILLIN AEROSOLS—HISTORICAL NOTE

In this issue there appears an article by Abramson touching on the history of penicillin aerosol therapy of the lungs. In view of the important role which this type of therapy has assumed and in view of the fact that the connection of penicillin aerosol with the War Department has never been published in detail, it seems desirable to give some of the material which the editor-in-chief has gathered together to clarify the history of penicillin aerosol therapy of the lungs.

The following summary is based upon the list of appended references.

In the fall of 1942, Dr. Abramson served as a medical officer on the staff of the Chief, Technical Division, Office of the Chief, Chemical Warfare Service. He was instructed to continue his early work in the field of aerosol therapy of the lungs by his immediate superior, Colonel R. W. Hufferd. In particular, as far as penicillin aerosol therapy was concerned, he was requested to apply his experiences with low-pressure generation of aerosols to certain phases of the general problem which confronted the Chemical Warfare Service at that time. These two phases were (1) development of nebulizers for use in the field for aerosol therapy of the lungs, following exposure to chemical warfare agents, and (2) development of methods for the treatment of secondary infections of the lungs in casualties due to chemical warfare agents, including those of importance in biological warfare. This, of course, included antibiotic therapy.

At a meeting held in Washington, August, 1942 (Abramson, Fremont-Smith, Hufferd), this program was discussed in detail and was implemented by a direct contract from the Technical Division of the Chemical Warfare Service to the Long Island Biological Association, Cold Spring Harbor, New York. In addition, support was given to this project by a grant from the Josiah Macy, Jr., Foundation, which had previously supported Dr. Abramson's work on aerosols and with which his broad program on germicidal and therapeutic aerosols had been discussed in detail before the war. On March 10, 1943, a meeting was held at Edgewood Arsenal, Maryland, on "Aerosol Therapy of Gas Casualties of the Respiratory Tract." Here, the feasibility of aerosol therapy of the lungs by antibiotics was discussed in detail, and tentative arrangements were made, with the assistance of the Macy Foundation and the Medical Division, to proceed with the experimental phase of penicillin aerosol therapy in animals and in man. Very shortly thereafter, many of the technical problems of aerosol therapy in man, in connection with the construction of and choice of nebulizers, appeared to be solved. Dr. Abramson then

directed the Cold Spring Harbor group to begin the study of penicillin aerosols in man. Thus, Bryson, who was assigned to the project, gives credit to Abramson for the initiation of the penicillin aerosol therapy program. He states in his report: "Perhaps the most interesting aspect of the work has been the development of penicillin mists for inhalation. We know that many serious lung infections are caused by bacteria susceptible to the action of penicillin. It appeared to our colleague, Major H. A. Abramson, MC, that the introduction of penicillin directly to the site of infection might give certain advantages over a conventional method of administering the drug. Clinical studies at the College of Physicians and Surgeons in New York City and St. John's Hospital in Brooklyn have confirmed the value of penicillin aerosols in the treatment of some kinds of chronic and acute pulmonary disease."

Bryson and his co-workers sent (in a confidential report) their well-known results on the successful application of penicillin aerosol to man to the Technical Division early in 1944. Their results were considered by Dr. Abramson and the Chief of the Technical Division, Brigadier General Kabrich, to be of such importance that Dr. Abramson organized and presided at a meeting of interested medical agencies and requested that the Cold Spring Harbor group report their findings to these agencies so that proper co-ordination could be made. This meeting on "Generation of Aerosols for Therapy of the Respiratory Tract" met on May 22, 1944, at Edgewood Arsenal, Maryland. Following is an abstract of the report of the minutes of this meeting.

Representatives from the following organizations attended the conference: Professional Services, Surgeon General's Office; Preventive Medicine, Surgeon General's Office; Medical Division, Office of Chief, Chemical Warfare Service; Bureau of Medicine and Surgery, U. S. Navy; Camp Detrick, Maryland; Office of the Air Surgeon; Chemical Warfare Laboratory, Ottawa, Canada; Medical Director, Macy Foundation; Biological Laboratory, Cold Spring Harbor, New York; the Aerosol Laboratory, Columbia University, New York (Division 10, NDRC); the Medical Research Laboratory, Edgewood Arsenal, Maryland; Medical Division, Office of the Chief, Chemical Warfare Service; Department of Medicine, Columbia University, New York.

The chairman (Abramson) opened the meeting by outlining the relationship of the Technical Division, OC-CWS, and Division 10, NDRC, to the aerosol program. Both of these agencies had had extensive experience with both large scale generation of aerosols as in screening smokes and in small scale work as in testing penetration of filters. Out of this interest in aerosols had come the desire to assist medical agencies in the development of equipment for the generation of theraputic aerosols whereever these medical agencies thought that such equipment was necessary. Reference was made to the program of the Cold Spring Harbor group which had been making a fundamental study of aerosol generation by

low-pressure metal, glass and plastic nozzles. Extensive studies of the control of particle size had been accomplished. In addition, the recent work on penicillin (supported by the Macy Foundation) was described by the chairman and presented, in detail, at the meeting. This work of the Cold Spring Harbor group on penicillin aerosols had reached a point sometime before where the results of the work on animals and man merited extended application to man. It was the purpose of the conference to co-ordinate and make available to medical agencies represented at the conference all of the facilities on aerosols of the Technical Division in so far as this was possible and acceptable.

The chairman pointed out that there were at least two types of aerosol therapy possible:

(1) Where low concentration effects were desirable, e.g., a small quantity of 1 to 100 epinephrine *nebulized* to relieve bronchial spasm; effect of penicillin on infections.

(2) Where high concentration effects were of interest, e.g., lining the respiratory tract or any portion thereof with *atomized* lipiodol. A procedure of this type might be desirable in the case of mustard burns of the trachea and bronchi.

It was pointed out in some detail that any substance which lowers the vapor pressure sufficiently would stabilize the droplets of an aerosol. Thus, therapeutic aerosols may be stabilized by a variety of such substances as glycerol, sugar, salt, urea, et cetera.

At this meeting action was taken as follows: "Study of penicillin aerosols will be undertaken at Columbia University in the Department of Medicine, by Dr. Barach, with the support of the Macy Foundation, in cooperation with the Technical Division and the Cold Spring Harbor group."

It must be emphasized that this meeting was the culmination of a long series of unpublished experiments on both animals and man on many phases of penicillin aerosol therapy and was an essential part of the teamwork which was needed to implement projects of this type during the war. Collaborating directly and acting as part of this team by invitation of the Technical Division, as indicated in the minutes, were Barach and his group. Their well-known paper on penicillin aerosol was published in the following year (1945). At about the same time, a most important paper appeared from the Mayo Clinic by Olsen.

Recognition of the role played by Abramson in initiating, organizing and directing the penicillin aerosol project for the War Department was made officially in Washington on October 24, 1946, when Major General Alden Waitt conferred upon Abramson the Legion of Merit, in the specifications of which are many of the details given in this summary of the history of penicillin aerosol therapy.

F.K.H.

REFERENCES

1. Abramson, H. A.: Improved inhalation therapy of asthma. Arch. Phys. Therap., 21:612, 1940.

2. Abramson, H. A.: A stable hydrogen peroxide aerosol. Science, 96:238, 1942.
3. Barach, A. L., Silberstein, F. H., Oppenheimer, E. T., Hunter, T., and Soroka, M.: Inhalation of penicillin aerosol in patients with bronchial asthma, chronic bronchitis, bronchiectases and lung abscess: Preliminary report. Ann. Int. Med., 22:482, 1945.
4. Bryson, V., Sansome, E., and Laskin, S.: Aerosolization of penicillin solution. Science, 100:33, 1944.
5. Chemical Warfare Service (Technical Division): Correspondence from 1942 to the present, concerning the penicillin aerosol project.
6. Chemical Warfare Service (Technical Division): Minutes of two conferences held at Edgewood Arsenal, Maryland:
"Aerosol Therapy of Gas Casualties," March 10, 1943.
"Aerosol Therapy of the Respiratory Tract," May 22, 1944.
7. Hufferd, R. W.: Penicillin aerosol: contribution of the Chemical Warfare Service to medicine. Science, (In press).
8. War Department: Unclassified records.

DEMEROL IN THE THERAPY OF ASTHMA

It is timely to call to the attention of our readers certain aspects of the dangers of the use of demerol for the therapy of asthma. In spite of the lay attitude, e.g., *The Reader's Digest,* regarding the use of this drug, allergists should recall, when using demerol, that patients with primary demerol addiction have recently been admitted to the United States Public Health Service Hospital for treatment. Indeed, demerol, since July 1, 1944, has been subject to the provisions of the Federal Narcotic Law and, as such, is under the same restrictions as opium, coca leaves, their salts, derivatives and compounds.

Inasmuch as it is widely recognized that habit-forming drugs of the opiate type are contraindicated in the therapy of asthma, it appears likely that demerol falls under the same restriction. Bronchial asthma is, *par excellence,* a chronic disease. To expose a patient with a chronic disease to the chance of becoming an habitué seems unwarranted. It is, therefore, recommended that demerol be used in bronchial asthma with the same restriction that applies to opium, coca leaves, their salts, derivatives and compounds. H.A.A.

BENADRYL—FURTHER COMMENT

Already there are numerous publications on the value of Benadryl in the treatment of asthma, hay fever and urticaria. Not only is the value of this compound in the treatment of these illnesses controversial but also the mechanism of its observed action. On the one hand, there have been claims that improvement occurs in the majority of cases of asthma. In the experience of many allergists Benadryl is practically of no value in asthma. Indeed, its depressant effect is possibly disadvantageous in reducing the cough reflex under certain circumstances. It is generally recognized and accepted, however, that a large number of patients react with drowsiness. Indeed, drowsiness occurs with therapeutically effective doses in as many as half of the patients who take it. That the anti-

histamine effect of Benadryl may be fictitious is brought out by pollen hay fever and asthma. The sneeze reflex is often reduced but the nasal congestion and the complication of asthma usually remain unchanged in too many cases. Let us examine the clinical pharmacology of Benadryl. In a series totalling 696 cases treated with Benadryl in recent literature, there were 366 instances of drowsiness. Indeed, the number of cases should be somewhat higher because certain of these patients took the drug only at bedtime. There is evidently a strong sedative reaction which should be viewed as a primary reaction rather than a "side reaction." In evaluating whether the Benadryl effects in asthma, hay fever and urticaria are due to an anti-histamine effect or due to a sedative effect, clinical tests must be made in which are employed narcotics, sedatives or hypnotics which produce drowsiness in approximately 50 per cent of the patients. Small doses of barbiturates and other drugs, which are commonly used, are comparable controls. We must ascertain whether, on a clinical basis, Benadryl is an anti-histamine drug or simply a depressant, which decreases the sensitivity of the patient's neurovascular mechanism, similar to other narcotics and hypnotics. Until these clinical controls are completed, clinical evaluation of Benadryl, as an antihistamine compound, is open to serious question, although its value as a depressant is definitely established.

Benadryl, no doubt, has a useful place in medicine as an adjuvant measure, but where this usefulness will lie is yet to be determined.

H.A.A.

Some Properties of Antigens and Antibodies

(Continued from Page 437)

bining capacity; chemists tell me that the oxygen atoms in CCA would tend to form weaker hydrogen bonds with proton-donating groups than the oxygen atoms in PABA where the presence of double bonds in the ring intensifies the drift of electrons. If the hydrogen bond be one of the intermolecular forces concerned in antigen-antibody union then its influence on specificity would appear to be more prominent in connection with early antibody, which was inhibited by benzoic acid but not by CCA. The nature of the altered mechanism of antideterminant-formation as immunization progresses remains entirely obscure.

In conclusion, immunochemistry is a fascinating discipline which makes use of unique and highly specific methods; it offers tools for the clearing and cultivation of the difficult domain of protein-chemistry in general; it can contribute richly to our effective understanding of disease and of many substances that are vital to the continuity of normal bodily function. Some of these potentialities will be more fully realized in the immediately forthcoming years.

Editorial Comment

CERTIFICATION IN ALLERGY

An announcement of certification in allergy by the American Society of Certified Allergists, a division of the American College of Allergists, Inc., through the American Board for the Certification of Allergists, appeared in the January-February, 1946, issue of the ANNALS OF ALLERGY. The purpose of this board is to certify physicians in the specialty of allergy. The need for this action is apparent, since allergy permeates so many special fields of medicine that any other method of certification would be inadequate. A cordial invitation was, therefore, extended to all allergists to join ranks and assume the responsibility which belongs solely to allergists, namely, the certification of physicians as allergists by allergists under the aegis of the American Society of Certified Allergists.

In spite of the high standards for certification set by the American Board for the Certification of Allergists, it was surprising to read the following editorials appearing in the *Journal of the American Medical Association* and the *Journal of Allergy.*

CERTIFICATION OF SPECIALISTS IN ALLERGY

Announcement was recently made by the American College of Allergists that a division called "The American Society of Certified Allergists" had established an "American Board for the Certification of Allergists." This "board" announces certain requirements which must be fulfilled for certification in this field, including provisions for a "founders group" to be admitted without examination. Provision is made also for the admission of others in exceptional instances to certification without examination.

The American College of Allergists, which is sponsoring this new movement, should not be confused with the American Academy of Allergy; the two groups are quite unrelated. The new proposal for certification is entirely independent of the well established procedures for certification by the recognized American boards in the various specialties. The recognized boards are sponsored by the national societies in each specialty and the corresponding section of the American Medical Association. They were organized after careful review of the advisability and need for the establishment of the boards. They have been recognized and approved by the Council on Medical Education and Hospitals of the American Medical Association and also by the Advisory Board for Medical Specialties. Certification by a regular board is indicated in the directory of the American Medical Association by an appropriate symbol. Since this new proposal for certification in allergy has not been considered by the Council on Medical Education and Hospitals of the American Medical Association or the Advisory Board for Medical Specialties, recognition of its certification will not appear in the Directory of the American Medical Association or in the Advisory Board's Directory of Medical Specialists. Neither has any provision been made for recognition of the new board in any of the official publications dealing with certification of specialists. There is now in operation an adequate mechanism for the regular certification in allergy as a sub-specialty of the American Board of Internal Medicine as well as the American Board of Pediatrics.

Any new group of specialists seeking recognition as a regular board should proceed through these accepted channels:

1. The proposal should be presented to the Advisory Board for Medical Specialties and to the Council on Medical Education and Hospitals of the American Medical Association.

2. Jointly these two bodies consider the proposal, including the need for a new board and the adequacy of the educational program and facilities for the proposed certification.

3. Official approval of the new board by the American Medical Association follows on approval by the Council on Medical Education and Hospitals on recommendation of the Advisory Board for Medical Specialties.

4. Official recognition of the board is indicated by listing the specialty in the "Essentials for Approved Examining Boards in Specialties," indicating certified specialists with an appropriate symbol in the Directory of the American Medical Association and in the Advisory Board's Directory of Medical Specialists, and admission of the board to membership in the Advisory Board for Medical Specialties.

5. Institutions seeking residency approval in the new field make application to the Council on Medical Education and Hospitals.

6. The Council conducts an inspection of the institution and prepares a report which is submitted to the new American board.

7. Approval of the educational institution occurs only by conjoint action of the Council and the American board involved.

The phenomenal growth of certification in the specialties is a clear indication of the need for this protection of the public and the profession in the field of specialty practice. The established procedures have operated unusually well and there is no indication that there is need for a departure from these procedures in allergy or in any other field. It is particularly unfortunate that this new group has incorporated the terms "American Board" and "Certification" in its title, since these terms have become identified with approved boards and their programs. This terminology is certain to mislead young physicians who seek to become recognized as specialists in this field.—*J.A.M.A.*, 131:599, 1946.

CERTIFICATION IN ALLERGY

In reply to many inquiries, the American Academy of Allergy desires to clarify the problem of certification in Allergy. At present, recognized certification in Allergy requires prior certification in Internal Medicine or in Pediatrics, followed by examination and certification in Allergy. Neither the American Board of Dermatology nor the American Board of Otorhinolaryngology has indicated its desire or willingness to certify in Allergy.

Wide publicity has been given recently to certification in Allergy by a self-constituted group which calls itself the American Board for the Certification of Allergists. This so-called board has no connection with the Advisory Board of Medical Specialties or with any of its constituent specialty boards sponsored by the American Medical Association. The American Board for the Certification of Allergists has failed to follow the established procedure of filing an application with or obtaining approval of the Advisory Board for Medical Specialties or of the Council on Medical Education and Hospitals of the American Medical Association. It is clear, therefore, that the American Board for the Certification of Allergists is not to be confused with the established certifying boards; neither will it replace, or act for or instead of, any of the established certifying boards. Furthermore so-called certification by this unofficial group will not be recognized by the Advisory Board for Medical Specialties or by any of its constituent boards, the Council on Medical Education of the American Medical Association, the American Medical Association, Hospitals, or medical schools. Under the circumstances, neither the Directory of Medical Specialists nor the Directory of the American Medical Association will include such certification.

EXECUTIVE COMMITTEE
AMERICAN ACADEMY OF ALLERGY
—*J. Allergy*, 17:248, 1946.

To clarify our position the following letter was sent to the editor of the *Journal of the American Medical Association*. This letter also serves as an answer to the editorial appearing in the *Journal of Allergy*.

The American Society of Certified Allergists
Division of
The American College of Allergists, Inc.

Sept. 19, 1946

Editor,
Journal of the American Medical Association,
535 N. Dearborn St.,
Chicago, Ill.

To the Editor:

The editorial on "Certification of Specialists in Allergy" by the American Society of Certified Allergists and American Board for the Certification of Allergists, a division of the American College of Allergists, Inc., which appeared in the *Journal* (131:599, June 15, 1946) requires clarification.

The American College of Allergists and its various divisions are in agreement with the statement appearing in the editorial, "The American College of Allergists . . . . . should not be confused with the American Academy of Allergy" and that the "American Board for the Certification of Allergists is entirely independent . . . . . of the recognized American Boards." We are independent. Independence is a characteristic of American culture. It is, therefore, natural that we should take unto ourselves the duty of bearing a united message of allergy—organizational, clinical and research—to American medicine. Because our position did not coincide with certain other important matters not mentioned in the Editorial, the American Society of Certified Allergists and its companion organization the American Board for the Certification of Allergists, were created by the American College of Allergists, Inc.

There are certain facts concerning the membership of the American College which should be more generally known. The American College of Allergists (many of its members are also members of the American Academy of Allergy) is the largest allergy society in the world. All members of the College are obliged to maintain their Fellowship in the American Medical Association. Whether an allergist maintains his membership in one allergy society or another is of no importance since the greater number of allergists are for the separation of the certification of allergists from the American Board of Internal Medicine and the American Board of Pediatrics. Our new and independent arrangements were organized after a careful review of the need for a society for certified allergists and also for such a society to sponsor a more inclusive board for certifying allergists. It must be emphasized that we, as allergists, are naturally more interested in the progress of the subject of allergy than remotely or closely related groups. We, as allergists, contend that the existing method of subcertifying allergists is not to the greatest benefit of the subject of allergy or to the physician who specializes in it.

What peculiar forces make allergy a subspecialty of internal medicine and pediatrics today and perhaps a subspecialty of otorhinolaryngology and dermatology tomorrow, is not easily understood. It is clear that a subcertification board in each specialty can only lead to confusion in establishing and maintaining high standards in research and clinical allergy. The American Society of Certified Allergists was originated specifically to remedy this situation.

Neither the American Society of Certified Allergists nor the American College of Allergists, of which the Society is an integral part, has any disagreement with any of the American boards certifying physicians in their respective basic specialties. On the contrary, the ideals and aims of the various American boards are wholeheartedly endorsed. Whereas the initial purpose of incorporating allergy as a subspecialty was well-meaning, it is timely to take inventory. In the light of present conditions it is not difficult to predict that the existing methods of subcertification, which we now know was a mistake, must undergo a change. Since plans to rectify this ineffective technique of certification were not in evidence, the American Society of Certified Allergists was formed in the belief that certification of allergists is a function and a duty of allergists only.

It is regrettable that the editorial under discussion may be taken as intending to classify allergists belonging to the American College of Allergists as personna non grata. The biased content of the editorial can possibly be explained by the influence of allergists who were either completely ignorant of the true state of affairs or refused to concede their existence. The reference in the editorial to our Founders Group and also to our provision for the admission of allergists to certification without examination in exceptional instances does not come with good grace. We were only carrying out for ourselves the very same method of procedure which had been applied in the creation of the basic specialties and subspecialties by the American Specialty Boards. Only highly qualified and recognized allergists are eligible for our Founder's Group. It is strange that as late as 1945 the American Board of Internal Medicine and its Advisory Council on Allergy deemed it necessary to confer certification in internal medicine and allergy without examination on a physician who for many years has been recognized nationally as a specialist in allergy.

The *Journal* (August 17, 1946) reported eighty-one physicians subcertified in allergy by the American Board of Internal Medicine. Of these, it can be approximated that since 1939, 70 per cent were certified in the Founder's Group or otherwise without examination and perhaps fewer than 30 per cent certified by examination over a period of about six years. It must be remembered that this data refers to a specialty widely represented in every phase of medical practice. These figures are illuminating.

The editorial's remarks concerning the need for adherence to the procedures cover-

ing the application for permission by the American Specialty Boards for the creation of a new specialty board and the plea for avoidance of confusion of the "young physician" over certification in allergy is not impressive. If this is the dictum of certain allergists then these men are doing a great service to the cause of temporary disruption among American allergists. However, it is also possible that these suggestions reveal that in certain official quarters there is beginning to be an awareness of what should be the desired objective—a balanced and equitable procedure for the certification of allergists. We chose the only possible decision in the situation as borne out by the attitude expressed in the editorial—a free choice—to autonomy—to advance research and clinical allergy by the formation of the American Society of Certified Allergists to sponsor the American Board for the Certification of Allergists.

We hope that the Advisory Council of the American Specialty Boards will accept in our favor the logic of the situation as it is and not permit a small group with opposing interests to retard the recognition of full certification in allergy. While it is not our place to advise the committee, we hope that it may be able to face the situation and recognize the righteousness of our program. All we did for allergists is what the majority of allergists wanted—autonomy in the matter of certification. The high standards of educational training requirements of the American Specialty Boards of Internal Medicine, Pediatrics and others, have been maintained. But we insist that the standards of practice of allergy must be set for allergists by allergists. From these seemingly tangled roots there must be an unequivocal solution to autonomy in certification for allergists. Reconciliation of the American Board for the Certification of Allergists as an autonomous board within the framework of the American Specialty Board is a just solution and the problem should not be too difficult to resolve. It is a task worth accomplishing since the alternatives are in disharmony with the needs of American allergy.

(Signed) M. Murray Peshkin, M.D., Secretary-Treasurer
American Society of Certified Allergists and
American Board for the Certification of Allergists,
Division of the American College of Allergists,
Inc.

The Journal of the
American Medical Association
535 North Dearborn Street
Chicago 10

September 27, 1946

Dr. M. Murray Peshkin
450 West End Avenue
New York 24, New York

Dear Doctor Peshkin:

Thank you for writing to us relative to certification of specialists in allergy.

Our editorial simply aimed to state the facts of the case so that physicians generally, as well as those who consider allergy as a specialty, would be aware of the point of view of the Council on Medical Education and Hospitals of the American Medical Association and also of the Advisory Board on Medical Specialties.

We do not undertake to include certification of physicians in our Directory or any of our other publications until they have been approved by the Advisory Board for Medical Specialties and by the Council on Medical Education and Hospitals of the American Medical Association.

Very truly yours,
(Signed) Morris Fishbein

The American Society of Certified Allergists
Division of
The American College of Allergists, Inc.

October 10, 1946

Dr. Morris Fishbein,
Editor, J.A.M.A.,
535 North Dearborn St.
Chicago 10, Ill.

Dear Dr. Fishbein:

It is most kind of you to open up correspondence on the very important subject of "Certification of Specialists in Allergy." We feel it is important to continue

your present interest on this subject. The issues involved were detailed in our reply to the editorial which appeared in THE JOURNAL (June 15, 1946). Our letter of Sept. 19, 1946, was specifically drafted as an answer to the editorial to clarify the position of the American Society of Certified Allergists, a division of the American College of Allergists, Inc.

We hope we may have your assurance that our answer to the editorial will be published in the Correspondence Column of THE JOURNAL. If it is contrary to the policy of THE JOURNAL to publish our answer to the editorial, please let me know as soon as possible.

Thanking you for your courtesies,

Very truly yours,
(Signed) M. MURRAY PESHKIN, M.D., Secretary-Treasurer.

The Journal of the
American Medical Association
535 North Dearborn Street
Chicago 10

October 12, 1946

Dr. M. Murray Peshkin
450 West End Avenue
New York 24, New York

Dear Doctor Peshkin:

Replying to your letter of October 10: I doubt that anything is to be gained by printing in THE JOURNAL the letter which you sent to us under date of September 19. THE JOURNAL's comment was planned only to give information as to the current status of the situation. The discussions as to the place of allergy and certification would more properly be held before the advisory board in the Medical Specialties.

Sincerely yours,
(Signed) MORRIS FISHBEIN

Comment and Résumé on the General Problem of Certification in Allergy

Since the time that the American Society of Certified Allergists made its formal announcement of Certification in Allergy in the ANNALS OF ALLERGY, numerous inquiries have been received concerning its status.

The American Society of Certified Allergists does not condone the present scheme of subcertification in allergy by the American Board of Internal Medicine or Pediatrics or any other board which should so subcertify allergy in the future.

Some time ago a group of allergists from the American Association for the Study of Allergy and the Society for the Study of Asthma and Allied Conditions now merged as the American Academy of Allergy, selected a group of allergists already certified in internal medicine without examination also for subcertification in allergy without examination, to form their Founders Group. The American Board of Pediatrics has recently accepted the same group of allergists with the same modus operandi to subcertify pediatric allergists. There is no doubt that other boards might do likewise. Thus, allergy already recognized as a specialty by the American Medical Association would soon lose much of its value to medicine as a functioning specialty.

The American College of Allergists, through its American Society of Certified Allergists, determined to avoid the obvious dangers in the present mode of subcertification in allergy and established an independent and autonomous American Board for the Certification of Allergists so that allergists can be recognized as specialists in allergy. Thus, there are now two different methods of certification in allergy: one, through subcertification

by the American Boards of Internal Medicine and Pediatrics; and, two, through certification by our independent American Board for the Certification of Allergists.

The literature on the subject of certification contains many comments pertinent to the discussion, thus: Dr. B. R. Kirklin, secretary, American Board of Radiology, Rochester, Minnesota, was assigned "to study the requirements for eligibility of candidates for examination and certification as prescribed by the various special boards, and to discuss reasons for divergences of these requirements from those recommended by the Advisory Board for Medical Specialties." (*J. A.M.A.*, June 7, 1941, page 2616). He stated that his net impression from this review was that "while there are a few instances in which certain requirements are perhaps rather lax, there are more instances in which the conditions for eligibility are unnecessarily stringent. These conditions may be defended on the ground that they were designed to raise standards of practice. I am sure that we all endorse this aim in principle and that all of us cherish high ideals, but we also have to consider the practical side and must avoid trying to force achievement of those ideals too rapidly. Unduly severe requirements seem to reflect the spirit of the guild and to suggest a desire to restrict the number of recruits in a specialty. . . . In our zeal to keep out incompetents we must not overlook the other duty . . . that of fostering certification of applicants who are really competent." Evidently, the system was considered inadequate five years ago and this status has not materially changed for the better during this time.

During the last six years, there has been an untoward growing disharmony among many of the leading allergists in this country because of the restricted methods of subcertification by the American Boards of Internal Medicine and Pediatrics. In this connection and in support of this point of view, it is most pertinent to quote a few excerpts from an article by Dr. Howard T. Karsner, the eminent pathologist of Western Reserve School of Medicine and University Hospitals and chairman of the American Board of Pathology, entitled "A Pathologist Scrutinizes the Specialty Boards" appearing in the *Journal of the American Medical Association* on July 5, 1941: "The scrutiny of the specialty boards at this time is sort of stock taking with hope of building up, advancing, and improving rather than with destructive intent. . . . Freedom of selection, freedom of research, freedom in curriculum and pedagogic methods all guarantee continued progress in medical education . . . nevertheless, certain boards have seen fit to interfere with the freedom of action of medical schools to the extent of imposing certain rigid requirements such, of course, as the type of internship. This is not the place to discuss the merits of such a program, but some of the rulings savor of arrogance and can safely be said to be arbitrary. To be sure, these boards are within their legal rights, but they have not the distinction and knowledge in the field of medical education that would justify this exhibition of power. It is to be hoped that the specialty boards will scrupulously avoid similar action."

In speaking of the dangers inherent in the situation, Dr. Karsner further writes: "The boards are entirely voluntary and their activities supported by fees of candidates. There is no subsidy by any organization that might "tie strings" to gifts. This means that the boards are independent except as to certain items of supervision by the Advisory Board and the Council on Medical Education and Hospitals. Admirable as is this independence, it carries with it the hazard of dogmatic decisions and autocratic operation. A prerequisite for this service is enthusiasm, an en-

thusiasm which may reach such emotional heights as to be prejudicial to the very objectives of its ardor. The enthusiast must ever guard against becoming a zealot. The boards should be aware of this danger and avoid setting standards at a level which could be attained only as senility begins to lay its heavy hand on intellect. The boards, however, have returned again to the policy of apprenticeship. It is difficult to see how any candidate can procure the required training unless he attaches himself to one or a few distinguished persons in the field. His novitiate over, he passes the examination and is certified as competent. He becomes a freeman, nominally if not actually, of the same standing as his teacher. The danger lies in the formation of a guild or, in modern terms, a labor union. The members of the board are representatives of the special societies, which these new freemen usually enter. They, therefore, reflect to some degree the views of the societies. No one could deny these organizations the right to look after the professional, economic, and social interests of their members, but if they form pressure groups they may well defeat themselves. The labor union has no place in the medical profession or any of its divisions, and if the specialty boards were to favor such a development they would do harm rather than good." He concluded by commenting upon their organizers: "They must, however, be constantly on guard that their authority is not transmuted into autocracy. 'The letter killeth, but the spirit giveth life.' "

An Advisory Board of Medical Specialties of the Council of Medical Education and Hospitals of the American Medical Association has brought the total number of boards to fifteen by advancing subsidiary boards of anesthesiology and plastic surgery to the status of full and independent boards. It is illogical for the American Board of Internal Medicine to include allergy in the field of a subspecialty along with cardiovascular diseases, gastroenterology and tuberculosis. The present day concept of allergic states is to be met with in every specialty. By far the majority of those members of the American College of Allergists and the American Academy of Allergy who have been subcertified as allergists obtained such certification without examination only after they had been certified as internists or pediatricians also without examination. To a lesser extent, this practice is still continued. However, since the establishment of the subcertification in allergy, an absurdly small number of allergists have been subcertified by examination as compared with allergists subcertified without examination. Of about 1,000 physicians practicing as allergists less than 10 per cent have been subcertified in allergy, and less than 3 per cent have been subcertified by examination to date.

The present plan of subcertification denying to a large group of physicians engaged in the specialty of allergy the same recognition accorded to other groups is obviously breaking down the confidence of other well-meaning specialties.

The important specialty of allergy has, therefore, not willingly submitted to an arbitrary relegation to a position of subordination as a "subspecialty," by a group obviously not representative of the active physicians in the specialty of allergy. No reputable allergist desires to be known as a subspecialist.

If Specialty Boards are to continue to serve the purpose for which they were originally organized, there should be a complete review of policy at intervals so that they may be adjusted to meet changing conditions.

There is evidently no purpose in consoling ourselves with an inspired statement in the editorial of the *Journal of the American Medical Asso-*

ciation on Certification in Allergy reproduced in the foregoing: "The established procedures have operated unusually well and there is no indication that there is need for a departure from these procedures in allergy or in any other field."

The American Board for the Certification of Allergists did not follow the present shackling procedure of filing an application with the Advisory Board for Medical Education and Hospitals of the American Medical Association because its efforts would have been fruitless. Moreover, the American Board for the Certification of Allergists does not wish to be identified with the present system of subcertification.

Our American Board for the Certification of Allergists is only "unofficial" so far as the present "established" system is concerned, but is as official as the present specialty "boards" of the American Medical Association which as Dr. Karsner says "are entirely voluntary and their activities are supported by fees of candidates." Under the circumstances, the new independent American Board for the Certification of Allergists will publish its own Directory of Allergy Specialists which, with its present standards higher than those for subcertification, is bound eventually to be the authoritative reference roster.

Aerosol Therapy of the Lungs and Bronchi

(Continued from Page 456)

24. Knott, F. H., and Clark, W. H.: Absorption of penicillin via the lungs. Lancet, 1:468, 1945.
25. Mutch, N.: Inhalation of chemotheraputic substances. Lancet, 2:775, 1944.
26. Mutch, N., and Rewell, R. E.: Penicillin by inhalation. Lancet, 1:650, 1945.
27. Olsen, A. M.: Nebulized penicillin: preliminary report on its role in the management of surgical bronchiectasis. Proc. Staff Meet., Mayo Clin., 20:184, 1945.
28. Olsen, A. M.: Proc. Staff Meet., Mayo Clin., 21:53, 1944.
29. Prigal, S. J.: Production of aerosols from medicated solutions. J.A.M.A., 131:398, 1946.
30. Prigal, S. J., and Speer, F. D.: A new method of aerosolization of penicillin and other medicaments for inhalation therapy. Bull. New York M. Coll., 8:21, 1945.
31. Segal, M. S., and Ryder, C.: Penicillin aerosolization in the treatment of serious respiratory infections: preliminary report. New England J. Med., 223: 747, 1945.
32. Siltzbach, L. E.: Penicillin therapy in a case of chronic suppurative bronchiectasis. J. Mt. Sinai Hosp., 12:825, (July-Aug.) 1945.
33. Stacey, J. W.: Inhalation of nebulized solutions of sulfonamides in treatment of bronchiectasis. Dis. of Chest, 9:303, 1946.
34. Van Wigh, A. M., and Patterson, H. S.: The percentage of particles of different sizes removed from Dust-laden air by breathing. J. Indust. Hyg. & Toxicol., 22:31, 1940.
35. Vermilye, H. N.: Aerosol penicillin in general practice. J.A.M.A., 129:250, 1945.
36. Wilson, C. E., Hammond, C. W., Byrne, A. F., and Bliss, E. A.: The control of experimental pneumonia with penicillin. 1. Comparison of inhalation and injection therapy. Bull. Johns Hopkins Hosp., 77:411, 1945.

For further data on urea peroxide therapy see:

Brown, E. A.: Studies on tissue tolerance to a new glycerol peroxide antiseptic solution. Ann. Allergy, 4:33, 1946.

Brown, E. A., Abramson, H. A., Gorin, M., Kauffmann, H. O., and Shanley, E. C.: The stability of urea peroxide in glycerol, ethylene glycol and propylene glycol. (In press.)

Brown, E. A., Krabek, Wilfred, and Skiffington, Rita: A new antiseptic solution for topical application. Comparative in vitro studies. New England M. J., 234:468, 1946.

Progress in Allergy

ALLERGIC SKIN DISEASES

Eczema (Dermatitis), Urticaria, Drug Eruptions

A Critical Review of Recent Literature

STEPHAN EPSTEIN, M.D., F.A.C.A.
Marshfield, Wisconsin

Eczema (Dermatitis)

I. ATOPIC DERMATITIS

Pathogenesis and Etiology. The pathogenesis of atopic dermatitis is discussed by Frank A. Simon.[172] Largely based on his well-known research and experiments about human dander in the etiology of atopic dermatitis, Simon comes to the following conclusions: The most important allergenic excitant of atopic dermatitis, thus far described, is human dander. The allergen reaches the sensitive tissue by penetration into the epidermis from without. Injury of the cornified layers of the skin, such as scratching, favors penetration of the allergen. Simon believes that atopic dermatitis is, at least in part, an *epidermal* manifestation of atopy. Contrary to prevailing opinion, he believes that the frequently associated *urticarial* reactions to foods, inhalants, and even human dander, are coincidental and irrelevant from an etiologic standpoint.

Simon's ideas in some ways are novel and revolutionary. He[173] believes we should restudy atopic dermatitis disregarding old concepts and prejudices, a request with which the reviewer is in full accord. Simon's concept of epidermal sensitization in atopic dermatitis is supported by other evidence which has been reviewed previously.[46,48] One of his principal arguments is that he is able to elicit delayed eczematous reactions following tests with human dander. In seven out of ten adolescents and adults, suffering from atopic dermatitis, scratch tests with extract from human dander would produce urticarial reactions. Ordinary patch tests were positive only in two of them. However, when a patch was applied on top of a scratch test, all but one would develop an eczematous reaction. Simon believes that the concept of human dander as an important allergenic excitant of atopic dermatitis accounts for several clinical characteristics of this disease. Among them the following: (1) the occurrrence of atopic dermatitis in infants who receive nothing by mouth except human milk; (2) the frequent therapeutic failure of dietary manipulations; and (3) the tendency of the disease to lessen when the patient is hospitalized. Simon's[171,172] studies are very interesting and important. However, the reviewer cannot agree with him that the accompanying urticarial reactions to food and other inhalants are always coincidental. Experience, based on a fairly large number of infantile eczema cases in a rural district, has proved conclusively in many cases the etiologic importance of foods and dusts. However, I agree fully with Simon that the route of the allergen for the dusts is probably largely through direct contact. The external penetration of allergens in atopic individuals again has been demonstrated by F. Herrmann.[91] With the aid of a new penetrating base called "intraderm," Herrmann produced transitory lesions resembling atopic dermatitis by inunction of atopic allergens, besides urticarial reactions elicited in this manner.

From the Marshfield Clinic, Marshfield, Wisconsin.

Robert Norrlind[131] devotes a monograph of 168 pages to a clinical-experimental study of the pathogenesis of atopic dermatitis with special reference to acute infections of the respiratory tract. He believes that infections and infectious allergy play a considerable part in the etiology and pathogenesis of atopic dermatitis. Norrlind comes to the following conclusion: acute infections of the respiratory tract, and probably also other infections such as periostitis alveolaris and cholecystitis, sometimes promote or aggravate atopic dermatitis in adults (39 per cent of his 100 cases). Nearly all these patients (thirty-seven out of thirty-nine) gave positive reactions to bacterial tests with mixed throat vaccines, whereas out of fifty-eight patients who did not experience exacerbations of their atopic dermatitis during respiratory infections, only seven reacted to these antigens, and mostly with faint reactions.

Sulzberger and Baer[189] find it noteworthy that few cases of atopic dermatitis become severly infected. They have not seen a single instance of severe invasive infection with staphylococci or streptococci in spite of their not inconsiderable experience with extensive, continuously scratched and traumatized atopic dermatitis. The reviewer agrees with this statement, at least as far as juveniles and adults are concerned, but occasionally he has seen serious secondary infection, such as erysipelas, in infants. In spite of the absence of invasive pyogenic infection, the reviewer believes that secondary infection and especially infectious sensitization play a very great part in atopic dermatitis of older children and adults. Skin tests with bacterial allergens have shown in many instances unusually severe reactions, especially with streptococcic antigens. The reviewer believes that the allergic state of the skin frequently masks the secondary infection. Therefore, infection does not produce the clinical picture of a pyoderma but that of an eczema. In my opinion, this bacterial allergic response acts as a protective mechanism accounting for the absence of severe invasive pyogenic infection.

Rowe[157] found in sixteen out of 180 cases of eczema of the hands, that inhalant pollen allergy was the cause. Dermatitis on the face, neck, and extremities and less often on the body may develop after the major dermatitis of the hands has recurred for several years. These patients give a history of a recurrence or exaggeration of the dermatitis of the hands during the pollen season. Skin tests, especially scratch tests, are frequently negative. Rowe advises hyposensitization with multiple antigens containing all important pollens in the air in the patient's environment during the month that the dermatitis exists. He recommends repeated small doses of weak dilutions from 1:5 billion (1:5,000,000,000) to 1:50,000. The role of food allergies in atopic dermatitis is stressed and exemplified by Turnbull.[203]

Psychobiologic Factors. The role of psychosomatic or psychobiologic factors in eczemas is stressed by several authors. Distinction is not always made between the different types of eczema, but most cases would fall under the broader concept of atopic dermatitis.

Clarence Bernstein[19] underlines the relationship between allergy and nervous fatigue. Illustrated by six case histories, the interplay of allergy and personality is demonstrated. The patients with "eczema" should be studied both for allergic exposures and situational, personality and environmental influences. Treatment should take both into consideration. Correction of the psychological factors hastens recovery. The author recommends sedatives, especially phenobarbital, mid-day naps, and suntanning for the patient. He found injections of 2 c.c. crude liver extract twice weekly helpful. If itching persisted or there was oozing, he gave 10 c.c. of 10 per cent calcium gluconate intravenously two to four times weekly. No major psychotherapy was undertaken since it was felt that this is the province of the specialist in that field. Much sympathetic counsel, however, is thought necessary.

According to Hodgson,[92] psychosomatic reaction in a patient with a hypersensitive skin may take the form of atopic eczema or pruriginous papular eczema affecting the forehead, cheeks and neck.

Kalz[99] discusses the role of psychological factors in skin diseases in general. The importance of the histamine-acetycholine mechanism in the pathogenesis of skin diseases cannot be overemphasized. Grant and co-workers have presented evidence that urticaria in their cases was produced by the release of acetycholine at the terminations of cutaneous nerves. Hopkins and co-workers described cases in which a generalized urticaria was produced by the following stimuli: (1) exposure to heat, partially or generally, (2) exercise, (3) emotional excitement, fear and anger, and (4) introduction of acetylcholine parenterally. Kalz observed identical reactions, substituting histamine for acetylcholine. The possible psychogenic correlations of allergic phenomena are still not well understood. Kalz[99] describes an interesting case of alleged allergy in which psychogenic influences were a decisive factor. The patient suffered from an asthma-eczema complex and was found to be sensitive to pork and lentils. Ingestion of minimal quantities of dialysates of this food protected him from asthmatic attacks and exacerbations of this eczema which otherwise occurred invariably after eating this food. This interesting case was posted for a demonstration before a medical society, and by mistake a different dialysate was given prior to a meal and found to have protective value. It was found then that any placebo had the same effect, provided the patient believed it to be the protective substance and, further, it was found that pork hash presented as veal did not cause an allergic manifestation while veal, chicken and other substances presented as pork caused violent attacks. Skin tests were inconclusive; and, finally, when the patient was told about his unscientific behavior, he gave up having asthma altogether.

There is little doubt that the psychobiologic side at present is overemphasized. However, there is one form of vesicular or dysidrotic eczema of the hands in which psychogenic factors play a great role, as has been emphasized time and again by Becker and Obermayer. Davis and Bick[39] present from the psychiatrist's viewpoint three such cases, one of them with other manifestations of an atopic dermatitis. From the history and by intentional creation of situations of stress and anxiety, it could be shown that emotions led to renewed outbreaks or flare-ups of the eczema. The skin lesions of atopic eczema and hyperhidrosis were considered part of a physiological manifestation of generalized anxiety, and no evidence of purely hysterical reactions were noted.

Laycock's[108] discussion of psychotherapy for the general practitioner may also be of value to the allergist. Most general practitioners hold aloof from the study of psychotherapy for many reasons. The author points out a few basic principles of psychotherapy. Patients may be ill as the result of the frustration of either their psychological needs or their physical needs: (1) The need for affection; to live in reciprocal warm regard with one or more human beings—parents, brothers and sisters, teacher, employer, friends or playmates. (2) The need for belonging; to be a desired and desirable member of a group—family, community, play group or work group. (3) The need for independence; to order reasonably one's own life, and to make one's own decisions.

There are two main attacks from the psychological angle on the symptoms displayed by the neurotic patient. These are: (1) to remove the patient from the strain causing the maladjustment, and (2) to remove the emotional strain from the life of the patient.

Hormones and Eczema. Hormonal influences in eczema, especially the atopic variety, are well known. Garnier[63] discusses the relationship of gonadal hormones to certain dermatoses in women. He presents two cases of long persisting chronic

eczemas of the hands. The skin of these patients never cleared up completely except during pregnancy. Both patients gave histories of premenstrual aggravation. Although these cases were clinically identical, one was cured with estrone and the other with progesterone. Garnier believes that in these cases there was a disturbance of balance between the follicle and the corpus luteum hormone. Garnier[63] presents the following considerations: (1) More dermatoses are related to hyperestrinism than to a deficiency (relative or absolute) of estrone. (2) The anti-estrogens (progesterone, testosterone) are more easily regulated than the estrogens, whose effects are sometimes paradoxical or unexpected. (3) While estrone is a very active substance, progesterone and testosterone are feebly acting anti-estrogens. One must use the latter in much larger doses than the former.

In certain cases, a dermatosis which has once yielded to, for instance, progesterone, can later become resistant to this hormone, and can be alleviated by estrone.

The following scheme can be used as a practical guide:

1. Dermatosis with intermenstrual exacerbations. (a) With evidence of hyperestrinism: Use testosterone as an anti-estrogen during the first ten days of the cycle, in doses of 10 mg., every other day for four or five injections. (b) With no evidence of hyperestrinism: Use moderate doses of estrone, for example, three to five injections of 1 mg. between the eighth and fifteenth days of the cycle. Beware of high dosage.

2. Dermatosis with premenstrual exacerbations: (a) Hyperestrinism is usually the cause; prescribe three to five injections each of 10 mg. of progesterone over the nineteenth to twenty-sixth days of the cycle. (b) Excess of the luteal hormone is sometimes present and may be absolute, or relative, due to estrone deficiency in the latter half of the cycle. It is in such cases that anti-estrogens have a paradoxical effect and provoke a premenstrual mammary swelling. Estrone should be used in relatively large doses, for example, 15 mg. in three injections over the last eight days of the cycle.

3. At the menopause: (a) Natural menopause: Use estrone, at first in small doses (1 mg. per injection), and progressively raise the dose to reach finally a total of from 10 to 20 mg. per month, depending on the symptoms and on the effect obtained. If estrone is badly tolerated (in women with menopausal hyperestrinism), change to testosterone giving three 10 mg. injections per week, every other week. Some cases may be found to react better to the acetate of testosterone than to the propionate.

Anal and Other Pruritis. Drueck[41] obtained rapid improvement in a case of periodic anal pruritus from intravenous and local therapy with penicillin. The latter was applied as wet packs, 250 units per c.c. Bodkin[24] estimates that in 95 per cent of cases of pruritus ani no observable lesions or disease can be demonstrated; in his series every patient was highly nervous. He found a high B. coli count in the stool, suggesting some inability to digest carbohydrates. Taka-diastase, 5 gr.; phenobarbital, ⅓ gr.; novatropine, 1/24 gr.; and dilantin sodium 1½ gr. were given in capsule form by mouth before each meal and upon retiring. Supplemental management included: cleansing of the perianal area with bland oils instead of soap and water; application of a silver nitrate solution to fissures; avoidance of alcohol, mineral oil, condiments, and fried foods. Most of his forty-two patients responded in a short time. Dobes, Jones and Franks[40] obtained favorable results in seven out of ten cases of senile pruritus with injections or inunctions of testosterone propionate. Usually 10 mg. were given at three to seven days intervals for ten to twelve injections; afterwards a maintenance dose of 10 mg. was injected every three weeks. Inunctions were carried out daily; the daily doses of the ointment contained 4 mg. of testosterone propionate. Oral adminis-

tration of methyl testosterone, 10 mg. three times a day, had no effect upon the pruritus.

Treatment of Atopic Dermatitis: Antihistaminic Drugs. The new antihistaminic drugs, benadryl and pyribenzamine, have aroused great hopes for the treatment of allergic skin diseases. An informative review about the history and physiology of these antihistaminic substances is given by R. L. Mayer.[120] The effects of these drugs in atopic dermatitis have not been as spectacular as in other allergic conditions. According to A. Schnitzer,[163] the older preparation "antergan" was not effective in atopic dermatitis and other eczemas. This drug had been used widely in Europe. The more modern preparations, available in this country, such as pyribenzamine (Ciba) and benadryl (Parke, Davis), are not only less toxic, but at the same time much more efficient. They exert a beneficial effect upon the pruritus of atopic dermatitis in about 60 to 70 per cent, although there is no general agreement as yet. Levin[110] obtained relief in six out of ten cases of atopic dermatitis with benadryl. Waldbott[210] noticed symptomatic relief only in two out of six cases of atopic dermatitis. Pyribenzamine[47] appears more effective in atopic dermatitis than benadryl. The relief of the pruritus and also its beneficial effect in acute exacerbations of atopic dermatitis were very impressive. Prolonged experience with severe cases of generalized atopic dermatitis (neurodermatitis disseminata) has indicated to the reviewer that even these chronic cases can be benefited by pyribenzamine. However, the results are a far cry from a cure.

Other Forms of Treatment. A new preparation, "Pepto-Sulfene," for the treatment of allergic dermatoses including atopic dermatitis, is recommended by Juon.[98] It is a coated tablet, the outer zone of which contains the peptone which dissolves in the stomach. The hyposulfites are contained in the core of the tablet and are only liberated in the alkaline juice of the intestine. This is a non-specific form of therapy.

Specific desensitization in cases of atopic dermatitis by daily inunctions of the allergen with "intraderm" were carried out by F. Herrmann.[91] No serious side effects were observed. Herrmann observed improvement, or nearly complete disappearance of lesions following inunction with allergens to which the patient reacted. Scratch tests and inunction tests became negative, the former usually earlier.

The treatment of the localized atopic dermatitis, also called lichen simplex chronicus or circumscribed neurodermitis, is discussed by Barber.[11] Athough the majority of these cases respond satisfactorily to fractional doses of x-rays or thorium X, combined with sedatives, rest, change of environment and psychotherapy, relief is usually temporary unless an estrogen is given. When the itching has entirely ceased, it is advisable to give a small maintenance dose. In the majority of the cases, Barber[11] chooses oral estrogens for convenience. Alpha ray-emitting preparations such as thorium X for the local treatment of circumscribed atopic dermatitis are also recommended by Burrows.[31] He uses 1,000 electrostatic units in alcohol or 1,500 units in varnish.

Theophylline ethylenediamine as an antipruritic agent is recommended by E. Epstein.[45] Theophylline ethylenediamine, when injected intravenously in a dose of 0.5 gm. in 20 c.c. of fluid, produces immediate relief in patients with generalized or localized itching. Twenty-five patients suffering from various types of itching dermatoses, including poison oak and other forms of contact dermatitis, disseminated neurodermatitis, exfoliative dermatitis, and localized eczema of the hands, experienced immediate relief of itching following one or more intravenous doses of theophylline ethylenediamine. The relief lasted from thirty minutes to twelve hours, the average being four hours. The injection was never repeated more than

once in a twenty-four-hour period. The mechanism by which this drug produces relief of pruritus has not been determined. The dangers of the promiscuous intravenous use of theophylline ethylenediamine, particularly in patients with impaired cardiac reserve, are stressed.

Infantile Eczema. Treatment of infantile eczema with fats rich in unsaturated fatty acids is again recommended by Hansen.[81] The combined experiences of Finnerud, Kessler and Wiese and that of Hansen and his co-workers reveal that over one-half of the patients with intractable eczema are greatly benefited by the dietary inclusion of fats rich in the unsaturated fatty acids. Another one-fourth or more appear to be benefited to some degree. In most of the recent studies, fresh lard has been the source of fat. Most patients appear to have little difficulty in taking lard in teaspoon or tablespoon quantities, although some prefer to take it with salads as dressings, on cereals, or as a spread on crackers, toast or in sandwiches. It is felt that a therapeutic trial should comprise a period of about two months or so, using 1 to 2 ounces per day. At the present time, it appears that this regimen should supplement but not substitute for a careful allergic work-up and the use of local therapeutic measures.

Johnson[95] recommends the use of large amounts of hapamine in intractable cases of infantile eczema. He reports very good results. In his series of eighteen cases, only one was not improved. Johnson found hapamine so helpful that he believes it should be tried more extensively. His patients were tested first intradermally with a 1:100 dilution of hapamine. If this test was negative, 0.2 c.c. of this dilution was used. At the next visit, 0.1 c.c. of undiluted hapamine was given subcutaneously. The dosage was increased by 0.1 c.c. at each subsequent dose unless there was a local reaction. Only a few reactions occurred, none severe. The dosage at which improvement was noticed varied. Sometimes 0.5 c.c. was the correct amount; commonly 1 c.c., and as much as 2 c.c. had been given in severe cases. These doses are in excess of the manufacturer's recommendation. Johnson injected the hapamine three times a week, as a rule, but sometimes more frequently.

Boric acid, generally considered to be a harmless and useful drug, is demonstrated by Watson[212] to be dangerous. He describes a case of fatal poisoning in an infant suffering from severe infantile eczema. The child had been treated with boric acid ointment. In three general applications, a total amount of between 60 to 100 gm. of the ointment containing 10 per cent boric acid, was used. The diagnosis of boric acid poisoning was made because of the fact that appearance, symptoms and clinical course resembled known cases of boric acid poisoning. The most remarkable symptom was the "boiled lobster" appearance of the whole skin. The application of the boric acid ointment to extensive areas of broken skin caused sufficient absorption to bring about acidosis and irreparable damage to the central nervous system. The small usefulness of boric acid does not seem to warrant the risk in accidental or intentional use.

Lamm[106] emphasizes again the danger of intramuscular injections of calcium gluconate in infants. This route should not be used.

According to Strickler and Ginsburg,[183] the sedimentation rate is of no diagnostic value in the eczema of infants. The authors believe, however, that the test has a definite purpose in predicting pyogenic infections or flare-ups.

Dangers of Intradermal Testing. The danger of intradermal tests in atopic individuals without preceding negative scratch tests is stressed again by reports of anaphylactic shock with fatal outcome.[195,217] Wiseman and McCarthy-Brough[217] report a fatal anaphylactic shock after intradermal tests in a woman seventy-eight years of age.

Another—nearly fatal—case of severe constitutional reaction in an asthmatic, following intradermal tests with caroid (papain) is reported by Osgood.[137]

Swineford reports two cases of anaphylactic shock in asthmatics, one of them fatal. In both cases, routine preliminary scratch tests with seventy-two commonly reacting allergens were negative. Swineford[195] concludes that every intradermal test should be preceded by the less sensitive scratch test. Even if this warning is based on unfortunate experiences with asthmatics, it might be a good rule also for patients suffering from atopic dermatitis, especially as some are actual or potential asthmatics.

II. CONTACT DERMATITIS

Mechanism of Sensitization. Several authors report experimental studies on contact type sensitivity. Olin[136] carried out sensitization experiments with 2:4 dinitrochlorobenzene. Single applications of a 10 to 30 per cent solution to a small area may cause sensitization of the entire skin. The primary reaction consisted in an erythema limited to the painted area. After a single application the hypersensitiveness manifested itself usually by a flare-up of the earlier erythema. Positive reactions appear earlier and stronger when closer to the painted area than in more distant parts of the skin. The author assumes that spreading of antibodies directly into the surrounding skin may play a role. Hyposensitivity may also occur in the proximity of the painted area. In some cases positive passive transfer is reported by the author. The reactions were stronger with persons who had been treated with the chemical but had not yet been sensitized. Olin[136] calls this a passive strengthening of sensitivity.

Rokstad[152] devotes a monograph of 352 pages to investigations of skin reactions from turpentine and hexanitrodiphenylamine. He comes to the conclusion that contact type (eczematous) sensitization is in all probability of an immunobiological nature, although it has seldom been possible to demonstrate with certainty the presence of antibodies in this form of sensitivity. The presence of humoral antibodies seems demonstrated by Haxthausen's[88] experiments with transplantation of sensitized skin. Of two pairs of identical twins, one of each pair was sensitized with dinitrochlorobenzene. After minimum sensitivity was established, pieces of skin of the sensitized individual were transplanted to the non-sensitized twin and vice versa. The result of patch tests, performed three weeks after the transplantation, was identical in both pairs of twins. The skin from the non-sensitized partner reacted after it was transplanted into the sensitized twin; whereas the skin from the universally sensitized twin lost its reactivity after it was transplanted into the non-sensitized partner. These results indicate that hypersensitivity cannot be due to a change in reactivity of epidermal cells nor to local antibody formation in the skin, but must be due to a factor conveyed to the skin from the sensitized organism, most likely a humoral antibody.

This viewpoint is further substantiated through Haxthausen's[86] experiments on "parabiotic" guinea pigs. Guinea pigs were sensitized with dinitrochlorobenzene. These animals (donors) were then united with normal guinea pigs (receptors) through operative parabiosis. From the fourth day following the union of the two animals, the receptor animals showed also positive reactions. These reactions were proportional to the degree of sensitization of the donor, but always somewhat weaker than that of the donor.

In contact dermatitis, the epidermis is usually considered the primary and main seat of the pathologic changes. Rockstadt[152] believes that histological investigation can hardly determine whether the epithelial changes are primary or whether they are secondary to the alterations of the blood vessels in the corium. From his functional investigations by means of "compression experiments" he concludes that "eczematous" (contact type) reactions are inhibited by pressure against the

skin, a phenomenon known in urticaria and light reactions. This would indicate that the tissue fluid involved in the contact-type reactions is derived primarily from the blood vessels and this makes it probable that the primary reaction in contact type dermatitis also occurs in the vessels of the corium.[152] This question is complicated by the fact that dermal sensitivity may be associated with epidermal sensitivity in actual contact dermatitis. Templeton[198] cites examples of co-existing epidermal and dermal sensitization in the same individual. Sulzberger and Baer[188] emphasize that the simultaneous occurrence of epidermal (eczematous) and dermal (urticarial) sensitization is much more common than is generally realized. We must, however, distinguish between two types of "dermal" hypersensitivity.[2] One, the "anaphylactic" or "atopic" or "urticarial" form of dermal sensitivity produces an immediate whealing response following a cutaneous or intradermal test. This is apparently the dermal sensitivity meant by Templeton[198] and Sulzberger and Baer.[188] Both authors agree that this form of urticarial sensitivity is most apparent in poison ivy dermatitis where the clinical picture frequently has an eczematous *and* urticarial component. The other form of dermal sensitivity is the delayed, inflammatory reaction, usually referred to by the dermatologist and allergist as "tuberculin-type" reaction. It has been also called "microbic type" reaction.[47] Epstein and Pinkus[50] believe that dermal sensitivity of the tuberculin-type reaction may be capable of producing clinical contact dermatitis. These authors stress that co-existing epidermal and non-atopic dermal sensitivity are encountered much more often than is generally recognized.

Becker[14] also recognizes the role of dermal hypersensitivity in contact dermatitis from nickel. However, in general, Becker connects dermal sensitivity to nickel and chromates with those forms of atopic dermatitis which he classifies as "functional dermatitis," such as dry neurodermatitis (atopic eczema), exudative neurodermatitis (nummular eczema) and pompholyx (dyshidrosis). As in the case of atopic dermatitis, further investigations are also necessary in contact dermatitis to establish definitively the mechanism and pathogenesis of their specific sensitization. It appears[47] that eczematous contact-type sensitivity and tuberculin-type sensitivity are immunologically very similar, if not identical. The principal difference seems to be the shock organ.

Specificity of Sensitization. The specificity of sensitization in contact dermatitis from the point of view of chemical configuration has always interested the dermatologist. Rothman, Orland and Flesch[156] investigated this problem by studying the group specificity of hypersensitiveness to procaine. They found that group specificity in epidermal allergy follows a pattern similar to that of serological reactions. Their patient reacted to procain, butyn, larocaine, pontocaine, monocaine and tutocaine. In their subject the allergic response required an antigen with the structure of a p-aminobenzoic acid ester, in which the alcoholic side chain contained a secondary or a tertiary amine nitrogen. The length of the side chain and the position of the tertiary amine nitrogen was not decisive. They observed an identical pattern of group specificity in a second case; however, the group specificity of both their subjects was different from those reported previously by other authors. When one remembers that the group specificity of a chemical as simple as iodoform (CHI_3) may be based either on the iodine molecule or the methyl group, it becomes evident that more complicated chemicals are likely to show more than one pattern of group specificity. Although I know of no specific studies on this subject, this apparently holds true for sulfonamides. It explains why some persons are sensitive to one sulfa drug only, for instance, sulfanilamide, but are able to tolerate a different sulfonamide, whereas other individuals are sensitive to several or all of the sulfonamides.

According to Rostenberg and Kanof[155] chemical reactivity or chemical structure

of the substance, or a combination of both, might determine the capacity to cause eczematous (contact type) sensitization. These authors experimented with 2-4-dinitrochlorobenzene. Their studies indicate a correlation between the geometrical resemblance of the molecules of related compounds and their capacity to produce reactions in sensitized individuals. The isomer which deviates the most from the parent compound gives the least reactors. Peck[141] believes that asymmetry influences the sensitizing mechanism. He found that the levo-rotatory fraction of nirvanol was more potent in producing drug eruptions than the dextrorotatory fraction. Sulzberger[186] reminds us that patients may become sensitized to substances they have never met, because these substances may be close or distant chemical relatives of the original allergen.

Contact Allergens. The frequency of contact dermatitis due to medication is well demonstrated in a report by Underwood and co-workers.[206] Forty per cent of 400 dermatologic patients showed positive patch-test reactions to one or more of the remedies used. The chemicals causing dermatitis most frequently were mercury, phenol and ethyl aminobenzoate.

L. Schwartz[166] discusses in detail the various skin hazards in people working with synthetic resins. Dermatitis is seldom caused by the completely polymerized, finished pure resin. The monomers and low polymers, and the incompletely condensed (cured) resin, or the uncombined products are the usual causes of dermatitis. The catalysts and the by-products may also be skin irritants. Eighty cases of sensitivity to rubber products are reported by Bonnevie and Marcussen.[26] They represented about 2 per cent of their material of contact dermatitis. Only twenty-five of these cases were occupational. Rubber footwear and articles were the dominating causes. The accelerator agents used in the manufacture, especially mercaptobenzothiazol, were the most frequent factors in sensitization. Cold-vulcanized rubber can often be tolerated where there is only accelerator-type sensitivity. Contact dermatitis with special reference to military personnel is discussed by Rudolph.[159] A case of contact dermatitis due to contact with the chrome 17 per cent steel identification tag of the U. S. Navy is reported by Harris.[82] Dermatitis in the American munitions industry, and the various explosives manufactured in the United States are discussed by Gant.[62] In dealing with powerful chemicals, such as explosives, the question arises whether one is dealing with a dermatitis due to primary toxic irritation or from allergic sensitization. Schwartz and Peck[167] emphasize that a substance that is a primary irritant in a strong concentration, may also be a sensitizer and thus produce a dermatitis in a weaker dilution. Lemon grass oil, according to Mendelsohn[123] is a primary irritant if its citral content is 75 per cent or over; in a dilution of 1:10 it produced reactions apparently only in sensitized persons. The interrelationship between primary irritation and allergic sensitization is well demonstrated in Goldblatt's[66] cases. He emphasizes that cases of an acquired hypersensitivity after an initial attack from a direct irritant are very common in the organic chemical industry. He noticed the establishment of hypersensitivity after the apparent healing of a vesicated skin and recommends special precaution in deciding on the return to work of the affected person. Goldblatt describes the powerful vesicant action of organic compounds used in the manufacture of poison gases. These substances are also potent sensitizers. In some cases photosensitivity ensued. Contact with sensitizing chemicals can also be accomplished by contaminated gloves or even straps from a wrist watch.

Schwartz and Peck[167] present an exhaustive review of dermatitis from wearing apparel. Those who are interested to know (as we all should be) the various and numerous chemicals and materials used in the manufacture of wearing apparel should read the article in the original. Lomholt[112] reports a case of a very severe

hypersensitivity to cell wool. This material has been used widely in the clothing industry in Denmark. Patch tests produced a severe reaction which turned into large excoriations.

Franks[60] discusses a case of contact dermatitis from Ace Adherent, proven by a positive patch test. Ace Adherent is a preparation used to obtain skin traction in amputees. In four cases out of several hundred, in which Ace Adherent was used, a dermatitis traceable to it was observed. Ace Adherent is composed chiefly of Galex (a rosin), Venice turpentine, tannic acid, gum camphor, and ethyl alcohol. Palmer [138] lists as more common contact allergens in the elderly patient the following: plants, soaps, industrial and household contacts, cosmetics, furs, animal hair and disinfectants. Among the rarer causes of contact dermatitis one might mention the case of Baer.[8] A physician who suffered from recurrent eczematous dermatitis of the hands and face was found to be sensitive to benzidine. With the advent of new and powerful insect-repelling chemicals, we must become aware of new sources of contact dermatitis. A case of dermatitis from DDT is reported by Niedelman.[127] Haxthausen[87] reports a case of allergic eczema caused by ethyl alcohol. It could be elicited by both epicutaneous application and by ingestion of a certain amount of alcohol. When the patient, a woman medical student, drank about two ordinary glasses of brandy (or more) the previously affected skin regions showed redness and swelling in the course of about twenty-four hours. Eczematous elements proper only seemed to appear after external application of alcohol. Patch tests with 5 per cent ethyl alcohol and higher concentrations gave a distinct eczematous reaction. These reactions were strongest at from 10 to 20 per cent, the intensity decreasing with increasing concentrations. Positive reactions were also found to methyl and propyl alcohol. Benzyl alcohol, isopropyl alcohol and glycerine gave negative reactions. It is comforting that cutaneous hypersensitivity to ethyl alcohol seems to be extremely rare. Haxthausen was unable to find a similar case in the literature.

We must realize that a contact dermatitis occasionally may act like any other non-specific stimulus in provoking specific lesions of a different type. I recall in this respect the recent observation of Kilpinen[102] where lupus erythematosus developed at the sites of a dermatitis due to sensitivity to a rubber mask.

Disability and compensation of occupational dermatoses, including industrial dermatitis, is discussed by Lane.[107] As Cleveland White[214] points out, in order to investigate intelligently the cause of industrial dermatoses the physician must have at least a sufficient knowledge of dermatology to distinguish a contact or occupational dermatitis from such ordinary skin diseases as psoriasis, impetigo contagiosa, urticaria, pityriasis rosea, lichen planus, acne vulgaris, and superficial fungus infections. A biopsy frequently helps to establish the proper dermatologic diagnosis. A cutting punch biopsy forceps is described by Walters.[211]

Poison Ivy Dermatitis. According to Mason,[119] the controversial nature of many recent publications dealing with allergy to poison ivy may be attributed in part to the lack of a standard allergenic substance and to experimentation with crude, unstandardized and unstable extracts. His report describes the synthesis in good yield of 3-n-pentdecyl-caltechol, an allergenic solid which has been shown to be present in the irritant oil of plants of the rhus genus. This is a stable crystalline substance. Inactivation of the allergens of poison ivy by tyrosinase has been attempted by Sizer and Prokesch.[174] This procedure is based on the reported detoxifying action of strong oxidants on the active principle of poison ivy extracts. Comparative patch tests with enzyme-treated and untreated ivy compounds on sensitized human and guinea pig skin showed a partial or complete loss of activity in the enzyme-treated material. The simultaneous application for four hours of poison ivy extract and tyrosinase produced a milder dermatitis than the application of

poison ivy and inactivated tyrosinase. In regard to the efficacy of poison ivy desensitization, the opinions are still divided. According to Stevens,[179] temporary desensitization can be achieved by the daily ingestion of large increasing doses of ivy extracts. There is clinical evidence, supported by statistics, that intramuscular injections have conferred resistance on susceptible persons. The treatment of the acute rash with poison ivy extracts should be discouraged because many patients are made worse, and there is no satisfactory evidence that any are helped.[179] A modification of extracts for the treatment and prophylaxis of poison ivy dermatitis is recommended by Margaret B. Strauss and W. C. Spain.[180] These authors used an aqueous suspension of the active resinous principles. The material used is an alum-precipitate which is relatively insoluble in water. This aqueous suspension was equally effective as alcoholic extracts both in regard to patch tests and therapeutic results. The aqueous solution can be administered more easily than oily poison ivy extracts. There is a further advantage of these suspensions because apparently larger doses at less frequent intervals may be given, as this new preparation is more slowly absorbed than the alcoholic extract. In the cautious dosage recommended by the authors (first dose between 0.2 c.c. of a 1:500 dilution and 0.1 c.c. of a 1:100 dilution) this extract did not produce any exacerbations of the poison ivy dermatitis. In a series of fifty patients treated by Niedorff[128] with the same extract 62 per cent obtained relief after the fourth injection, and 95 per cent after the sixth injection. Of twenty-five persons treated with an oily poison ivy extract, 60 per cent obtained relief after the fourth injection, and of twenty-five patients treated with an alcoholic poison ivy extract, 64 per cent obtained relief after the sixth injection.

Pratt and Corson[146] confirmed in the main the older findings of Sulzberger and Katz[193] that the fluid from blisters of dermatitis due to poison ivy does not contain a skin-irritating substance. In two instances they observed positive results. However, the authors refrain from definite conclusions because there was a chance that poison ivy extract (from the provocative patch test) might have contaminated the vesicle liquid.

Sunlight Sensitivity. There are cases of plant dermatitis in which sensitivity to sun light plays a role. Dermatitis of the hands due to photosensitivity from a substance contained in parsnip roots is reported by Vera Starck.[177] Toland[200] observed a case of a severe dermatitis from sunlight which apparently was cured following treatment with hapamine. A photo-allergic eruption following the ingestion of a sulfonamide is described by Burckhardt.[30] This author who had sensitized himself experimentally with sulfanilamide and light, developed a papular dermatitis of exposed parts after he had taken dimethylbenzoyl-sulfanilamide. Sunlight sensitivity also plays a role in the so-called meadow grass dermatitis (Oppenheim's dermatitis bullosa striata pratensis). Duckworth[42] presents four such cases in young girls. The day after a sunbath on a meadow, the patients developed an itching dermatitis of the exposed parts which later turned into the typical eruption. This consists of strikingly linear bullous lesions on an erythematous base. Contact with the grass and exposure to the sunlight is required to produce this phyto-photodermatitis.

Eczema of the Hands. Dermatitis of the hands is not always a contact dermatitis, as it is still thought to be by many. Eczema of the hands as manifestation of atopic allergy to pollens[157] has been mentioned above. Ferrer Zanchi and Bonduel[56] report a case of an erythematous vesicular dermatitis of the hands apparently caused by inhalation of vapors from aniline dyes. Such an etiological relationship is supported by Feinberg and Watrous[54] demonstration that simple chemicals may act as anaphylactic antigens. Anderson[4] suggests that palmar lesions may be

caused by a few of the well known and commonly used drugs. The sulfonamides, especially sulfapyridine, the iodine- and bromine-containing compounds, antipyrine, arsenic and gold compounds and insulin have been reported responsible for palmar lesions. Since the majority of these agents are used in the therapy of chronic diseases, their influence on such lesions might well be overlooked unless the history of each patient is taken carefully. We all have difficulties with many cases of hand eczemas. Frequently a great number of etiologic factors are responsible.[46] Eczema of the hands, as Goodman[72] puts it, is a diagnosis of ignorance. The management of recurrent vesiculopustular eruptions of the hands (and feet) is discussed by Carpenter.[33] He advances the theory that in many patients bacterial allergens may activate recurrent vesiculopustular eruptions in areas of skin which previously had been infected by, or sensitized to, fungi. Carpenter recommends for these cases vaccines that contain both fungous and bacterial antigens. The role of bacterial factors is also supported by the sometimes beneficial effect of penicillin or other antibiotics in what appears to be contact dermatitis.[207] It is this interaction of factors that makes difficult a specific diagnosis of many cases of eczema of the hands. Forman[57] emphasizes the importance of morphologic distinction of the eczematoid eruptions of the hands, both among the various groups and from other conditions of the hands, like acrodermatitis continua or Andrew's "bacterid." He reproduces the Senear-Hecht classification of vesicular dermatoses of the hands.[57]

Topical Treatment. Topical treatment of dermatitis is discussed by Goldsmith,[71] Polano[145] and H. Goodman.[73] Goldsmith presents a short review regarding indications for various ointment bases. In regard to penetration into the skin, the following vehicles penetrate particularly well:[71] oleic acid, cod liver oil, lanolin; and slightly less well: arachis oil, avocado pear oil, castor oil and olive oil. According to Polano,[145] cold creams should be made with true fats and weak emulsifying agents. The usual pastes can be improved by partial substitution of zinc oxide by zinc stearate. Guild[80] reminds us that the use of soap during the treatment of contact dermatitis may prolong the irritation after the direct cause has been eliminated even if the soap is not the etiological agent.

Patch Tests. A new technique for performing quantitative patch tests is described by Dunn, Mason and Smith.[43] It is applicable to sensitizing compounds that are soluble in volatile solvents such as acetone or alcohol. This technique should be useful in the study of cross sensitivity of chemically related compounds and to measure accurately the effectiveness of desensitizing procedures in contact-type sensitivity. Statistics about patch tests are discussed by Henderson and Riley[90] as well as Lila F. Knudsen.[103] Patch tests have also been employed to detect and evaluate the skin sensitizing capacity of chemical agents and materials, a procedure which Schwartz and Peck[167] have called the "prophetic test." Henderson and Riley[90] present statistical considerations in regard to this form of patch tests. Their mathematical formulas are based on bio-statistical principles for the correct interpretation of experimental tests. With the help of these formulas the likely maximum rate of positive reactions for the population can be predicted.

III. MICROBIC ECZEMAS

These include bacterial, fungous and other parasitic eczemas.

Microbic or infectious eczemas are still a neglected subject. The importance of bacterial sensitization in atopic dermatitis has been referred to above[131], also the role of both bacterial and fungous sensitization in eczemas of the hands.[33] Infectious eczemas are discussed by Török;[201] these eczemas may be caused by direct action of pyococci, or by an allergic reaction to these micro-organisms. In these

allergic cases, secondary pyrococcic invasion of an eczematous inflammation does not cause a purulent serous exudate but merely produces an increase of the inflammation and of formation of blisters and weeping. Sezary[168] makes a similar distinction. He calls the direct action of bacteria as manifested in pyodermas "orthoergic" in contradistinction to the "allergic" response when the skin becomes sensitized to its normal saprophytes or to extraneous organisms. The occupational microbic eczemas are characterized according to Sezary by chronicity and failure to disappear when the worker has been removed from his work; the lesions do not necessarily affect the whole exposed area. Patch tests are negative in "primary" microbic eczema. These eczemas are rebellious to ordinary bland applications, but respond to antiseptics even while the patient remains at his work. Boe[25] emphasizes that the allergic factor has not been duly considered in pathological conditions due to staphylococcic infection. He sensitized rabbits by means of intravenous injections of formalin-killed staphylococci. The sensitized animals could be desensitized only by intravenous injections of the vaccine or a culture filtrate, but not by subcutaneous or intradermal injections.

A generalized allergic skin eruption in a veterinary surgeon from infection with Brucella abortus (Bang) is reported by Lomholt.[111] During the past six to seven years the patient had been suffering continually or at short intervals from an extensive allergic Brucella exanthema of hands and arms, especially when delivering infected cows. Finally the patient experienced an attack of a generalized papular and acneiform eruption, covering also face and trunk. There was a severe tuberculin-type reaction to an intradermal test with Brucellagen. Serologic reactions always had been rather weak.

Generalized dermatitis from pediculosis capititis is reported by Ronchese.[153]

Penicillin and Tyrothricin. The great part that pyogenic infections play in eczemas is attested to by the large number of reports dealing with local applications of penicillin and other antibiotics or antiseptics.[28,58,68,77,89,100,122,209] Kierland[100] reports good results from wet applications of penicillin, 200 units per c.c., or ointments containing 200 units per gram in infected contact dermatitis and non-infected eczematoid dermatitis. Boulay[28] treated successfully with penicillin cream four cases of long standing external otitis and retroauricular intertrigo. Waisman and Gots[209] report poor results with penicillin ointments in infectious dermatitis, including infectious eczematoid dermatitis, infected dermatoses, dermatitis repens, and dermatitis of the ear canal. The results are partially explained by the fact that penicillin-resistant staphylococci were predominant among their patients with infectious dermatitis. Gotschalk et al.[77] also report disappointing results with penicillin ointment in nummular eczema, although the secondary infection responded to the treatment. Ten per cent of their cases treated with penicillin ointment developed a contact dermatitis from this source.

Parenteral penicillin therapy, with an average dose of one million units in five days, cured thirteen out of fifteen cases of impetiginous dermatitis in Manson's[116] experience.

In spite of difference of opinion regarding the efficacy of topical penicillin, it is safe to state that this method did not bring about any great revolution in therapeutics. In a given case, topical penicillin may work better than other antiseptics, but in general, penicillin ointments or creams are not superior to other antiseptics used for local application. The great value of penicillin therapy depends entirely on parenteral administration. There are numerous reports of sensitization to penicillin from external application which will be discussed in the chapter on drug eruptions. These papers as well as everyday experience indicate that sensitization occurs most frequently in infectious eczemas. In view of these facts, penicillin should not be used externally in otherwise harmless skin conditions except when really indicated.

Tyrothricin has the advantage over penicillin that sensitization with this drug is of lesser consequence because it is not used internally. Franks, Dobes and Jones[59] report dramatic results in eight cases of impetigo contagiosa treated with wet dressings and ointments containing tyrothricin. All of the eight cases responded on an average of six days and were cured. Improvement was noted in all three cases of pyoderma and the two cases of dermatitis repens. In other cutaneous infections only limited benefit was observed. Unfortunately, there was no improvement in five cases of nummular eczema and acrodermatitis perstans. In the opinion of the authors tyrothricin is of little practical value in the treatment of ordinary diseases of the skin. Only superficial inflammatory eruptions may be adequately treated, and secondarily invaded eruptions may respond, especially if caused by staphylococcus and streptococcus.

Sulfonamides. The indications of sulfonamide treatment in dermatology, its usefulness and abuses are discussed by Brunsting[29] and Tobias.[199] Sulfonamide ointments should never be used in cases of contact dermatitis with secondary infection since local sensitization is already present. Sulfonamide therapy should be reserved for skin conditions resistant to other forms of therapy or where withholding it might result in serious infection or unnecessary scarring.[199]

Fungous Eczemas. It is well known that what is generally called epidermophytosis of the feet is not an entity. Even excluding other conditions causing the clinical picture of "athlete's foot," such as contact dermatitis, bacterial infections, there are several fungi that produce somewhat different clinical manifestations. Montgomery and Casper[125] try to correlate the cutaneous manifestations of ringworm of the feet and nails with the invading fungi. In their material from New York, cultures showed the following fungi: Trichophyton gypseum, 65.4 per cent; Trichophyton purpureum, 15.7 per cent; Monilia albicans, 13.5 per cent; Epidermophyton inguinale, 2.8 per cent.

According to these authors,[125] in a majority of the infections by a particular organism, certain features predominate so it is possible in most cases to predict the invading fungus without culturing. Trichophyton gypseum, which is responsible for the largest number of infections, causes an acute inflammatory type of dermatophytosis in which vesiculation is the main feature. In the non-inflammatory type of dermatophytosis, trichophyton purpureum is the usual causative fungus. The plantar surface is the common site of infection, although it may involve the side or dorsa of the feet, toes and toe nails. This non-inflammatory type of dermatophytosis is more apt to be bilateral and symmetrical than the acute type caused by T. gypseum. In infection of the feet with monilia (candida) albicans, the characteristic manifestation usually limits itself to the interdigital webs. The skin between the toes is bright red, weeping and fissured at the base. Exfoliated and macerated skin is present at the borders of these denuded or red areas and overhangs it. This infection usually involves both feet and all interdigital webs. Epidermophyton inguinale, a cause of ringworm of the groin, also invades the feet. Proper treatment and prognosis depends to some extent on recognition of the causative fungus. In cases caused by Trichophyton gypseum or Epidermophyton inguinale the treatment must be varied according to the clinical manifestation (as outlined in last year's review.[46]) In T. purpureum infections, stronger fungicidal remedies are indicated. In Monilia albicans infection 3 per cent aqueous gentian violet or brilliant green, 5 per cent silver nitrate and 5 per cent ammoniated mercury ointment are the drugs of choice. Peck and Rosenfeld[142] had found that organic fatty acids occurring in sweat have a considerable fungicidal action without any irritating effect. Sulzberger, Shaw, and Kanof[192] found undecylenic acid-zinc undecylenate superior to sodium propionate in the prophylaxis and treatment of dermatomycosis. Ac-

cording to Shapiro and Rothman,[170] the undecylenic acid-zinc undecylenate cream tested by those authors is only slightly superior to sulfur-salicylic acid preparations. However, the undecylenate ointment is non-irritating and can be also used in patients with vesiculation, erosions, fissures and edema of the feet. Nickerson et al.[126] recommended wearing of sandals for patients with dermatophytosis of the feet. These authors believe that sandals help by preventing accumulation of sweat and by forming good cutaneous circulation through ventilation and free movement of toes.

IV. VARIOUS OTHER ECZEMAS

Cases of dermatitis that are based on co-existing epidermal and dermal (anaphylactic) sensitivity are reported by Templeton.[198] As "eczema autolytica" (*sic*) Smith[175] describes a generalized erythemato-vesicular eruption which occurs especially after a persisting eczema of the legs. Smith believes that this eruption is caused by a bloodborne dermolysin. We are still ignorant about the causes and mechanism of such dissemination. The reviewer believes that they are probably based on co-existing dermal non-atopic sensitivity similar to dermatophytids which they resemble a great deal.

There is still very little known about the influence of extraneous factors on eczemas of unknown origin. An interesting case is reported by Witherspoon.[218] This author describes a case of exfoliative dermatitis with an associated amebic dysentery. The dermatitis which had not yielded to treatment for three years showed a 90 per cent improvement in six weeks when amebiasis was discovered and properly treated. Though eosinophilia is not commonly associated with amebic infection, the blood picture showed 10 per cent eosinophiles.

Many other factors than allergy participate in the causation of the various forms of eczema, such as mechanical, physical, metabolic, hormonal and psychobiological factors. Occasionally eczemas are due entirely to them or nearly so.

Peck and Clare[140] conclude that maceration of the skin and subsequent secondary infection are the cause of the dermatitis seen in women processing potatoes for dehydration. The role of mechanical factors in the causation of dermatitis is well brought out in a paper on the effect of glass fibers on the skin by Leder.[109] A typical eruption occurs in persons working with glass-silk or glass-wool. It is characterized by disseminated pinhead-sized, red, highly itching papules, localized mostly on the inner aspects of the forearms. Histologic examination shows that they are caused traumatically by penetration of minute glass splinters into the epidermis and partly also in the pilo-sebaceous follicles. Experimental application of such glass splinters to the skin of patients suffering from eczema usually produced the same papular lesions. In one case a typical eczema developed. Leder[109] assumes that this was not a sign of hypersensitivity to glass fibers but due to fixation of circulating antigenic factors by means of mechanical trauma of the skin (Kogoj-effect). Sulzberger and his co-workers[191,194] have demonstrated the role of physical influences in the mechanism of dermatitis through their studies on so-called prickly heat carried out in Guam. A combination of cooling and drying remedies and of those which produce desquamation is recommended by the authors. Local applications of the following lotions were found most useful:

A	B
Menthol 1 per cent	Menthol 2.0
Glycerin 1 per cent	Camphor 2.0
Salicylic acid 4 per cent	Bismuth subnitrate 10.0
Alcohol 90 per cent q. s.	Zinc Oxide 10.0
	Alcohol
	Lime water aa q. s. ad 240.0

The starch iodine test which demonstrates the perspiration on the surface of the skin showed uniformly that exudation of sweat was either absent or significantly

reduced in the areas occupied by the lesions of prickly heat. The histologic studies indicated that the inhibition of sweating was presumably not due to impairment of the sweat glands to produce sweat but rather to difficulties in its excretion. The orifices of the sweat glands appeared covered or occluded by hyperkeratosis. There was also an inflammatory reaction and edema constricting the terminal part of the ducts. Z. Felsher and Stephen Rothman[55] found tremendously increased values of insensible perspiration in a case of exfoliative dermatitis that may be attributed to either the arterial hyperemia present or to the accelerated keratinization.

Metabolic factors of various forms of eczemas are discussed in Urbach's[205] new book on skin diseases, nutrition and metabolism. Endocrine factors and hormonal treatment are most apparent in atopic eczemas and have been discussed with that chapter. The effect of endocrine substances on the adult human scalp has been studied by Rony and Zakon.[154] The androgen testosterone had a stimulating effect, and the estrogen stilbestrol had a depressing effect, on the sebaceous glands of the adult male.

Vitamins. There is still quite a controversy about the part vitamins or vitamin deficiencies play in eczemas. Vitamins may be beneficial generally; as Tolliffe[97] states, the physician can contribute decisively to the preservation and the improvement of his patient's health by judicious nutritional advice and the appropriate prescription of supplementary and therapeutic levels of vitamins. Skin diseases due to vitamin deficiencies are discussed by Urbach.[204] The role of vitamin A in keratosis pilaris is not clear, according to Stannus.[176] Ichthyosis is frequently a factor underlying eczema. The response of ichthyosis to large amounts of vitamin A is again attested by Gordon.[75] Obermayer and Frost[133] attribute the beneficial effect of vitamin A in "nummular eczema" to the fact that these patients often have dry skins. Vitamin B complex therapy in seborrheic dermatitis and other forms of eczema is again recommended by Allison.[3] Mashkilleison and his co-workers[118] observed remarkable results in seborrheic dermatitis with daily doses of 100,000 units of vitamin A. But 5 mg. of riboflavin given three times daily for one to four weeks gave also relief in seborrheic dermatitis. The same authors[118] recommend vitamin B_1 especially in eczema because of its stimulating effect. Niacin relieved completely the itching in ten cases of eczema. Niacin as a vasodilator in certain eczemas is recommended by Schmidt.[162] Gougerot[78] reports a case of an exfoliative dry dermatitis which was clearly influenced by vitamin C. The dermatitis resembled a psoriasiforme parakeratosis. The history revealed a diet deficient in vitamin C. Treatment with 300 mg. of ascorbic acid brought definite improvement within ten days. A discontinuation of vitamin C brought about a recurrence of the dermatosis which was controlled by resumption of the therapy. After the dose had been increased to 500 mg. the regression of the lesions became more rapid and the condition cleared up nearly completely. Mashkilleison and his co-workers[118] report gratifying results in nine cases of chronic eczema treated with large amounts of ascorbic acid, 300 mg. intravenously or 600 mg. orally daily.

Oral vitamin therapy apparently always has been a harmless procedure, although allergic reactions especially to the fish oils containing vitamin A and D are well known. Reingold and Webb's[149] report of sudden death following intravenous injection of thiamine hydrochloride is certainly a warning against unnecessary parenteral vitamin therapy. Their patient had been given four injections at short intervals prior to death. Following the last injection she complained of a generalized burning, perspired profusely, became dyspneic and cyanotic, and died.

Urticaria

A case of urticaria from perfume is reported by Zakon and Kahn.[220] The patient suffered from chronic urticaria for six years. Collection and liberal use of

perfumes were her hobby. After one week of living in an atmosphre free from perfume, her hives disappeared, but re-occurred when again exposed to perfumes. This paper contains valuable notes on the composition of perfumes. Urticaria due to occupational contact with trinitrotoluene is reported by Preston and Watkins.[147] Patch tests with this substance produced, within a few minutes, a local urticaria at the site of the test. This is an interesting example of urticaria produced by external contact. Turnbull[203] presents a series of cases of urticaria due apparently to food allergies. According to Coca[34] chronic urticaria is frequently a symptom of familial non-reaginic food allergy.

Generalized urticaria with other signs of a systemic reaction following a bee sting is described by Obermayer,[134] urticaria combined with dermatitis from caterpillars by Berkowitz.[18]

Bivings[20] reports a series of twenty-two cases of acute urticaria in children, associated with acute infections. The characteristic picture was an urticarial eruption of varying intensity, usually edema of the hands and feet, and fever. In nineteen cases acute throat infection was the focus, in two cases acute otitis media, and in one pyelitis. Six throat cultures did not show the same organisms in any two cultures.

URTICARIA PHOTOGENICA

Two cases of urticaria from sunlight have been investigated by Blum, Baer and Sulzberger[22,190] and Blum, Barksdale and Green.[23] The case of Sulzberger and Baer[22,190] was produced only by wave length shorter than about 3700 Å. In this case a passive transfer was positive. The passive photosensitivity had the same wave length limits. The authors suggest that the antigen in this and similar cases is some normal constituent of the body produced or liberated in human skin by certain wave length of solar energy. The case of Blum, Barksdale and Green[23] differs from the foregoing inasmuch as it was produced by blue and violet light, wave lengths 4000 Å to 5000 Å. It is interesting to note that this patient experienced difficulties in a room lighted by fluorescent lighting. Failure of passive transfer differentiates this type of urticaria solare from that which is caused by shorter wave lengths. Hapamine did not alter the sensitivity to light in the second[23] case.

URTICARIA FROM COLD

Pellerat and Murat[143] have demonstrated that the normal histamine content of the skin amounts to about 20 mg. per kg. These authors find it difficult to explain why such a quantity of histamine does not provoke any trouble while very small doses of histamine introduced intradermally are liable to cause important tissue reactions. It is therefore necessary to assume that the histamine in the tissues is inactive and becomes active only upon liberation. It appears that this liberation may occur following minimal irritations. Pellerat and Murat[143] suggest that one might explain the mechanism of urticaria from cold by liberation of histamine in a particular terrain. Urticaria from cold has been treated successfully with benadryl.[53,132]

TREATMENT

Treatment of urticaria prior to the use of antihistaminic drugs is reviewed by Tate.[197] Intestinal antiseptics such as sulfaguanidine offer new therapeutic possibilities in urticaria due to intestinal bacterial putrefaction. Tate believes these cases are not uncommon. The diagnosis is suggested by a history of constipation and the presence of indican in the urine. Tate gives 3.5 gm. sulfaguanidine four times daily for a week or less.

The greatest advance of the past year in regard to urticaria has been the introduction of antihistaminic drugs, benadryl and pyribenzamine. Their efficacy, both in

acute and chronic urticaria, has been extolled in a number of publications: Arbesman, Koepf and Lenzner,[6] Baer and Sulzberger,[9] Curtiss and Owens,[37] Epstein,[47] Eyerman,[51] Feinberg and Friedlaender,[53] Friedlaender and Feinberg,[61] Levin,[110] Lynch,[115] O'Leary and Farber,[135] Shaffer, Carrick and Zackheim,[169] and Waldbott.[210] From the various reports it appears that in acute urticaria about 90 to 95 per cent may be relieved, whereas in the chronic form about 75 to 80 per cent are benefited. The effect is frequently dramatic; however, most investigators stress that pyribenzamine and benadryl afford only symptomatic relief. The reasons why some cases of urticaria do not respond are not known. The usual dosage of both benadryl and pyribenzamine is 50 to 100 mg. three times a day; however, larger doses may be given when necessary. In other instances smaller amounts may suffice. Both drugs are rather well tolerated. However, a number of side effects have been reported, chiefly sleepiness or drowsiness and dizziness. Less frequently dryness of the mouth, nausea, and diarrhea have occurred. With the normal dosage of 50 mg. three or four times a day, these side effects usually are mild. This holds true for both benadryl and pyribenzamine. However, these side effects are less frequent with pyribenzamine. Arnold[7] recommends cautious small amounts of benzedrine to counteract the undesirable drowsiness from benadryl during the daytime. During the night the sedative effect of these drugs frequently is not undesirable. Dermographism also responds well to benadryl[53] and to pyribenzamine. Although these drugs are highly specific against histamine, both are also mildly effective against acetylcholine[219] and probably possess additional pharmacologic qualities as evidenced by their sedative action. They seem effective also in cholinogenic urticaria,[47] a condition which is very resistant to treatment. According to Nomland,[130] cholinogenic urticaria is precipitated by heat and also by exercise and emotional stress. Nomland distinguishes two groups: those who have urticaria and those who have generalized itching without urticarial lesions. Hughes and McAlister[93] report a case of generalized urticaria following the use of protamin zinc insulin. Treatment with hapamine produced prompt relief of symptoms. According to Hartman,[83] widespread urticaria may be a symptom of flea bites in hypersensitive persons. Hartman obtained good results with hapamine in a series of twenty-two patients who suffered from persistent local or generalized reactions to flea bites. Successful desensitization to flea bites by means of an extract from fleas of cats, dogs and human beings is claimed by Hatoff.[85] Of 129 susceptible infants and children, 78 per cent were benefited. Bartelheimer[12] treated several hundred cases of acute urticaria by insulin shock with good results. A. A. Epstein[44] finds that urticaria is associated more commonly with hypothyroidism than with hyperthyroidism. Treatment of the hypothyroid state had a beneficial effect.

LICHEN URTICATUS (PAPULAR URTICARIA)

This common disease of childhood is characterized by small wheals which, subsiding in the course of a few hours, leaving hard itchy papules, papulovesicles or occasionally small bullae. According to Tate,[197]it is not ordinary urticaria modified by some peculiarity of a child's skin, but a separate condition with a different etiology. Tate believes the exciting agent is not food but some obscure factor in the child's home environment. He recommends avoidance of overclothing, adequate ventilation of the child's bedroom, restriction of carbohydrate intake, correction of digestive disorders, a soda and rhubarb mixture and antipruritic applications. Hüllstrung[94] believes that lichen urticatus may be caused by various single or combined factors. External factors such as foods and insect bites, and internal allergens, for instance, from intestinal parasites, may play a role. In most instances it is a complicated problem.

Drug Eruptions

PENICILLIN

There are numerous reports about skin eruptions following the use of penicillin. Although these allergic reactions are frequently generalized and distressing, penicillin can still be considered a rather safe drug. With one possible exception,[216] there was no report about a fatal case. There are many types of skin reactions to penicillin based on various forms of sensitivity. No doubt, more than one antigen is involved in the various types of allergic reactions.[52] Some patients are actually allergic to penicillin, others to impurities of the commercial products.

There are several reports about contact dermatitis from penicillin: (Goldman, Friend and Mason,[70] Markson,[117] Michie and Bailie,[124] Satulsky,[160] Schultz,[165] and Vickers.[208]) The ease with which patients may become sensitized by external application of penicillin becomes apparent from a study by Gottschalk and Weiss.[76] Patch tests with a penicillin ointment on 200 volunteers sensitized 4.5 per cent of them. Goldman and his co-workers[70] found sixteen cases of contact dermatitis from penicillin ointment therapy in about 350 cases of various dermatologic conditions. Patch tests were positive in ten out of twelve cases. Goldman[69] reports a vesicular cheilitis with edema of the lips following application of a solution of sodium penicillin. Benkwith,[16] Markson,[117] Schultz,[165] and Satulsky[160] report cases of contact dermatitis of the eyelids from instillation of penicillin into the eye. Sensitization may occur even from the use of weak preparations of a chemical. But stronger and, especially, irritating concentrations are much more prone to cause hypersensitivity. Michie and Bailie's[124] case is an example. A soldier's wound was treated with diluted penicillin solution on September 24 and 25; on October 2 and 5 undiluted sodium penicillin powder was introduced into the wound on the leg without any bad effect. On October 11, nine days after the use of the undiluted penicillin, two drops of penicillin solution (100,000 units in 5 c.c.) were instilled into both ears on account of otitis media. Within seven hours both ears were discharging profusely, the leg, previously almost healed, showed an acute weeping dermatitis. A patch test produced a similar reaction. However, not all cases of penicillin dermatitis by external contact are contact dermatitis (epidermitis) in an immunologic sense. There are cases reported of so-called contact dermatitis from penicillin with negative patch tests.[70,96,165] In Bedford's[15] case the patch test on normal skin was negative; a positive reaction was obtained only at the site of previous lesions. In these cases we may deal with localized sensitivity. Epstein and Pinkus[50] believe that they may be based on a different form of sensitivity, namely, on tuberculin-type sensitivity (non-atopic dermal sensitivity). These authors[50] present a case of vesicular "dysidrotic" dermatitis of the fingers from external contact with penicillin with negative patch tests but positive tuberculin-type reactions to intradermal tests with commercial penicillins and crystalline penicillin G. Both epidermal and non-atopic dermal sensitivity apparently were responsible for the dermatitis in Truitt's[202] case. His patient gave a positive patch test as well as a tuberculin-type reaction. Tuberculin-type sensitivity to penicillin was first described by Rostenberg and Welch.[155(b),213] This tuberculin-type sensitivity may be the immunologic background of the relatively frequent "dysidrotic" eruptions following parenteral penicillin therapy. However, the relationship between penicillin administration and the appearance of vesicular "dysidrotic" eruptions of hands and feet is not clear. The frequent simultaneous or past occurrence of dermatophytosis in many of these cases is noted by several writers. In Kolodny and Denhoff's[104] cases, concomitantly performed trichophytin skin tests were positive in nine out of fifteen penicillin-sensitive patients, whereas of fourteen non-reactors only five showed a positive trichophytin test. Graves, Carpenter and Unangst[79] had advanced the theory that in some instances the dysidrosiform lesions might result from liberated

toxins from foci of infection to which the patient was sensitive. Such an assumption is supported by the report of Schnurman[164] who presents five cases of latent trichophyton infection activated by parenteral or oral penicillin therapy. Lamb[105] considers also the possibility of an alteration of local immune balance. Bechet[13] believes that eruptions occurring in patients with an antecedent chronic dermatophytosis of the feet represent not allergic manifestations, but "some form of immunologic disturbance."

Urticaria from penicillin is reported by several authors.[182,202,221] Strickland's[182] patient also had severe angioneurotic edema. In Zeller's[221] and Truitt's[202] cases, intradermal tests and passive transfer were positive, but became negative later on. In Truitt's case, even a patch test produced a hive, again an example of urticarial reaction from external contact. Zeller's case illustrates well variations of the degree of sensitivity. During the reactive phase as little as fifty units of commercial penicillin sodium produced urticaria, whereas during the week following the cessation of symptoms increasing doses of penicillin up to 25,000 units caused no reaction. This observation seems rather important. It would help to explain apparently refractory phases in urticaria. In some instances, a patient with chronic urticaria will tolerate at times without difficulty allergens that usually cause urticaria. The theoretical aspects of the urticarial type of penicillin sensitivity are discussed by Rostenberg and Welch.[155(b)] Urticaria is usually also present in the so-called serum sickness-type reaction. Such reactions are described by several authors.[35,74,84,148,181,185]

Three cases of delayed "serum sickness" type of penicillin reactions are described by Gordon.[74] The characteristic features of this type of reaction appear to be (1) delayed appearance following the cessation of penicillin therapy, (2) intense, severe, generalized urticaria, (3) multiple involvement of joints with pain, (4) malaise, fever, tachycardia, (5) terminal exfoliative dermatitis of both palms, and (6) a self-limited course of seven to ten days. Both Feinberg[52] and Gordon[74] stress the resemblance of this picture to that of delayed reaction to liver extract and insulin. This serum sickness-type reaction sometimes is a rather serious affair. Wilensky[216] considers this anaphylactic sensitivity as the cause of the fatal outcome of his case. However, the fact of the high postoperative fever of this case leaves some doubt as to the part penicillin sensitivity played in this instance.

Observation of a definite photodermatitis in a patient treated both with sulfonamides and penicillin, leads Canizares[32] to believe that penicillin may be a photosensitizer; however, serious doubts have been raised against this interpretation.[49]

ATABRINE (QUINACRINE HYDROCHLORIDE)

Drug eruptions attributed to atabrine enjoy a lively interest at present.[187] These eruptions were noted first among military personnel in the South Pacific and presented a rather puzzling lichenoid picture. Full descriptions of this form of drug eruption have been presented by various authors[10,17,38,67,129,161,187] under the title of atypical or unusual lichenoid dermatitis, tropical lichen planus-like disease or similar headings. The incidence of this atabrine eruption is low. Even in groups with the highest atabrine consumption, only one in several thousands of the men was affected.[187] According to Bereston,[17] the eruption begins on the dorsal surfaces of the extremities with eczematoid lesions which soon develop into either chronic eczematoid lesions, lichen planus-like lesions, or both. The whole body may be involved. Either type may develop into a generalized exfoliative dermatitis. The principal features which make this drug eruption unusual are the variegated appearance, the polymorphic lesions, the long-lasting pigmentation and atrophic changes.[187] The histopathology is discussed by Bereston.[17] The eczematoid type shows histopathological resemblance to psoriasis. Goldberg[67] states that the microscopic changes in general are similar to those often seen in lichen planus. Schmitt

and his co-workers[161] have pointed out the clinical variations which differentiate this atabrine eruption from real lichen planus. The evidence that this syndrome is a form of drug eruption based principally on hypersensitivity to atabrine suggests that this condition should be called "atabrine eruption" or "drug eruption due to atabrine."[187] However, atabrine is not the only factor involved in the causation of this syndrome. Dietary deficiency, climatic and other environmental factors, and photosensitivity may play important roles.[17] There is a controversy about the mechanism of the atabrine sensitivity in these cases. Patch and intradermal tests performed in a few of Goldberg's[67] cases were negative. Agress[1] reports positive patch tests in cases of exfoliative dermatitis from atabrine. Dantzig and Marshall[38] who report on another series of twenty-four cases of "tropical lichen planus," gave several of their patients atabrine again in suppressive or therapeutic dosage after they had returned to the United States. This did not lead to allergic skin manifestations. Goldberg[67] made the same observation. Dantzig and Marshall[38] assume that no drug allergy existed, but they consider the possibility of drug toxicity. But in others' experience,[161,187] administration of atabrine to a group of patients with quiescent lesions caused a high percentage of focal flare-ups of the eruption or widespread eczematoid and exfoliating reactions. These reactions in some cases occur within the first day of re-administration, in other instances only after atabrine has been re-administered for several weeks.[187] The observation that many patients suffering from this lichenoid form of atabrine eruption have tolerated further medication of the same drug without new outbreaks or flare-ups has a parallel in some cases of arsenical dermatitis. It is well known that eruptions caused by arsenic and bismuth may present similar lichenoid lesions.[67] In these lichenoid psoriasiforme eruptions also, the connection between the drug and the eruption may be more complicated and less evident. Wiessema[215] describes sixteen cases of such lichenoid eruptions from prolonged treatment with arsphenamine which represent a close parallel to those from atabrine. Only one of Wiessema's cases gave a positive patch test. Intradermal tests were negative. He observed several times flare-ups of these "eczematids" (Darier) following arsenical treatment. He also reports a case that started as a lichenoid dermatitis and turned eventually into a generalized dermatitis. In other cases arsphenamine treatment could be continued without damage. Two similar cases of lichen planus-like eruptions from neoarsphenamine have recently been presented by Sylvest.[196]

Treatment of the lichenoid atabrine eruption follows conventional dermatologic procedures.[17] The use of atabrine is stopped. Strong or irritating drugs often aggravate the condition. Bereston recommends additional vitamin B complex therapy. Parenteral penicillin is recommended for the secondary infection.[17,129] Improvement occurs in two to eight weeks after withdrawal of atabrine.[161] The prognosis for life is considered excellent by Bereston.[17] However, one of Nisbet's[129] patients died from septicemia which developed from secondary infection. Agress[1] reports severe hepatitis from atabrine concomitant with exfoliative dermatitis; three of his Chinese patients died from this complication. Gillespie and Brown[64] report four cases of severe blood dyscrasia from atabrine sensitivity, characterized by agranulocytopenia, thrombocytopenia and anemia. Two cases were associated with atabrine eruptions. Three patients died, the fourth could not be traced.

Sugar and Waddell[184] observed an ochronosis-like pigmentation in ten individuals who had been treated with atabrine for a considerable period of time. The pigmentation involved the skin, hard palate, nail beds, cartilages of the nose, ears, epiglottis, and trachea. There was also pigmentation of the conjunctiva and the corneoscleral limbus. Lutterloh and Shallenberger[114] also report eight cases of unusual pigmentation following treatment with atabrine. This pigmentation should disappear within a period of six to nine months.

Fluorescence of the fingernails and toenails from atabrine is described by Kierland

and his co-workers[101] and by Ginsberg and Shallenberger.[65] This brilliant yellow-green fluorescence is exhibited under the Wood filter. Ginsberg and Shallenberger stated that patients receiving numerous other drugs showed no unusual fluorescent phenomenon under Wood's light. Kierland and his co-workers found that the light emitted by fluorescent nails had a wave length between 5,400 and 6,000 angstrom units. Normal nails exhibited very little fluorescence but on spectroscopic measurements showed a fluorescent band between 4,800 and 5,800 angstrom units. These authors also could demonstrate the presence of atabrine in the hair, nails and skin.

SULFONAMIDES

The pathology of anaphylaxis due to sulfonamide drugs is discussed by Black-Schaffer.[21] The dangers from the external use of sulfonamides are pointed out in a report of the A.M.A. Council on Pharmacy and Chemistry.[150] A so-called fixed bullous eruption from sulfathiazole is reported by McGuire and Shaffer.[121] The lesions were located on the mouth, penis, trunk and extremities. Passive transfer with blister-fluid from the site of a healed lesion was positive, giving both an immediate urticarial and a delayed reaction. Robitzek[151] adds a fatal bullous reaction to diasone. The eruption was pemphigoid in character with cherry-sized bullae. The probable immediate cause of death was bronchopneumonia and asphyxia.

MISCELLANEOUS

An excellent comprehensive article on drug eruptions is presented by Sulzberger and Baer.[187] Exfoliative dermatitis following arsphenamine therapy is reported by Costello and Laudy.[36] Bonnevie[27] presented three cases of an extensive polymorphous eruption from neoarsphenamine. Patch tests were positive in all three cases; in one instance the reaction was vesicular, in the other two it consisted of redness and follicular papules.

Rubin[158] reports a case of an allergic reaction after inoculation with typhus fever and yellow fever vaccines. The patient suffered from angioneurotic edema of eyelids, nose, and cheeks and in the chest. He was sensitive to egg yolk, but not to egg white. The yellow fever vaccine is prepared from infected chick embryos, while typhus vaccine is prepared from infected yolk sacks. The author does not want to decry the use of these important prophylactic agents, but wants to draw attention that allergic manifestations from them may occur in egg- and chicken-sensitive patients. Cautious administration of the vaccine, by giving it in small increasing doses and by having epinephrine and a tourniquet at hand, should be practiced. Allergy to egg-prepared vaccines is also discussed by Park.[139]

The role of nonspecific factors in drug allergy has been mentioned above with reference to the atabrine eruptions. Petersen[144] believes that the "state of atmosphere" is the most common and significant environmental factor and tries to prove this in presenting a series of cases from the literature. He tries to correlate the important clinical data with the meteorograms. Changes in temperature, both ways, sometimes at the time of the administration of the drug, sometimes at the moment of the appearance of symptoms are correlated with the clinical data. While nobody can deny that atmosphere conditions exert a considerable influence on the physical condition of the body, it seems doubtful that they were of such importance especially in the allergic cases analyzed by Petersen.

TREATMENT OF DRUG ERUPTIONS

The antihistaminic drugs, benadryl and pyribenzamine, have been used successfully in some cases of drug eruptions. They have also been employed prophylactically in cases of insulin sensitivity.[6,47] The secret has been lifted partially about a new drug which has proven its value in arsenical poisoning and dermatitis. Its name BAL stands for British Anti Lewisite. Longcope and his co-workers[113]

treated twenty-one cases of acute or subacute arsenical dermatitis. The dermatitis in seven was caused by contact with DM (Adamsite) powder and in fourteen by arsenical preparations used for the treatment of syphilis. The dermatitis cleared up satisfactorily in the seven patients with DM intoxication and in nine of the syphilitics; in the latter the skin returned to normal within an average of twelve and one-half days. In four of the remaining patients the dermatitis lasted from twenty-nine to fifty-three days after treatment was started, while in one patient, complicated by multiple infections, the dermatitis persisted for eighty days. State and Wangensteen[178] introduced procaine intravenously for the treatment of delayed serum sickness. Along with the relief of pain, subsidence of all the manifestations of serum sickness occurred in a large percentage of the patients treated. The procaine was given in doses of 1.0 gm. in 500 c.c. of normal saline over a period of two hours. In a total of twenty-seven patients treated, there were no untoward reactions. Appelbaum, Abraham and Sinton[5] confirm the striking result of this treatment in a case of serum sickness from antitetanus serum.

REFERENCES

1. Agress, C. M.: Atabrine as a cause of fatal exfoliative dermatitis and hepatitis. J.A.M.A., 131:14-21, 1946.
2. Albrecht, F. K.: Clinically important skin tests. Current Medical Digest, 15:26, (July) 1946.
3. Allison, J. R.: South. M. J., 38:235, 1945.
4. Anderson, Hamilton H.: Drugs and palmar dermatoses. J.A.M.A., 129:766, 1945.
5. Appelbaum, E.; Abraham, A., and Sinton, Wm.: A case of serum sickness treated with procaine intravenously. J.A.M.A., 131:1274-1275, 1946.
6. Arbesman, Carl E.; Koepf, George F., and Lenzner, Alfred R.: Clinical studies with N'-pyridyl-N'-benzyl-N-dimethylethylene-diamine monohydrochloride (pyribenzamine). J. Allergy, 17:275-283, 1946.
7. Arnold, Harry L.: Benadryl in chronic urticaria. Arch. Dermat. & Syph., 54:71, 1946.
8. Baer, R. L.: Dermatitis from benzidine. J.A.M.A., 129:442, 1945.
9. Baer, R. L., and Sulzberger, M. B.: Pyribenzamine in the treatment of itching conditions. J. Invest. Dermat., 7:147, 1946.
10. Bagby, J. W.: A tropical lichen planus-like disease. Arch. Dermat. & Syph., 52:1-5, 1945.
11. Barber, H. W.: Dermatoses of the menopause. Practitioner (London), 156: 333-346, 1946.
12. Bartelheimer, H.: Insulin shock in the treatment of urticaria. München, med. Wchnschr., 91:286, 1944.
13. Bechet, P. E.: Induced sensitivity from the topical use of the sulfonamides and penicillin. Pennsylvania M. J., 49:417, 1946.
14. Becker, S. Wm.: A new interpretation of some so-called positive patch tests. J. Michigan M. Soc., 45:65, 1946.
15. Bedford, P. D.: A case of penicillin dermatitis. Brit. M. J., 1:51, 1946.
16. Benkwith, K. B.: Allergy to penicillin calcium topically in blepharoconjunctivitis. U. S. Nav. M. Bull., 46:279, 1946.
17. Bereston, E. S.: Lichenoid dermatitis. J. Invest. Dermat., 7:69-83, 1946.
18. Berkowitz, S.: Caterpillar dermatitis. Bull. U. S. Army Med. Dep., 4:464-467, 1945.
19. Bernstein, Clarence: Allergic neurodermatitis. Urol. & Cutan. Rev., 49:684-688, 1945.
20. Bivings, Lee: Acute infectious urticaria. J. Pediat., 28:602-604, 1946.
21. Black-Schaffer, B.: Pathology of anaphylaxis due to sulfonamide drugs. Arch. Path., 39:301, 1945.
22. Blum, H. F.; Baer, R. L., and Sulzberger, M. B.: Studies in hypersensitivity to light. II. Urticaria solare (λ 3700). J. Invest. Dermat., 7:99, 1946.
23. Blum, H. F.; Barksdale, E. E., and Green, H. B.: Urticaria solare (λ4000-5000A). J. Invest. Dermat., 7:109, 1946.
24. Bodkin, L. G.: Am. J. Digest. Dis., 12:255, 1945.
25. Boe, John: Investigations on the importance of bacterial allergy for the development of cutaneous infections due to staphylococci. Acta dermat.-venereol., 26:111-136, 1945.

26. Bonnevie, P., and Marcussen, Poul V.: Rubber products as a widespread cause of eczema. Report of eighty cases. Acta dermato-venereol., 25:163-178, 1945.
27. Bonnevie, P.: Extensive polymorphous neosalvarsan exanthemas. Acta Dermato-venereol., 25:534-535, 1945.
28. Boulay, G. H.: Penicillin cream of low concentration. Brit. M. J., 1:50, 1946.
29. Brunsting, L.: Sulfonamide treatment in dermatology. M. Clin. North America, 844-848, 1944.
30. Burckhardt, I. W.: Photoallergisches Exanthem nach Irgafen. Dermatologica, 91:249-252, 1945.
31. Burrows, A.: Radio-active substances in the treatment of diseases of the skin. Practitioner (London), 156:364-369, 1946.
32. Canizares, Orlando: Is penicillin a photosensitizing agent? Arch. Dermat. & Syph., 52:17, 1945.
33. Carpenter, C. C.: Management of the recurrent vesiculopustular eruptions of the hands and feet. J. M. Soc. New Jersey, 42:262, 1945.
34. Coca, A. F.: Dermatologic manifestations of familial nonreaginic allergy. Ann. Allergy, 3:101-109, 1946.
35. Cormia, F. E.; Jacobsen, L. Y., and Smith, E. L.: Reactions to penicillin. Bull. U. S. Army M. Dep., 4:694, 1945.
36. Costello, M. J., and Laudy, Simeon: Dermatitis exfoliativa following arsphenamine therapy. New England J. Med., 232:369-373, 1945.
37. Curtis, A. C., and Owens, B. B.: Beta dimethylaminoethyl benzhydryl ether hydrochloride (benadryl) in treatment of urticaria. Arch. Dermat. & Syph., 52:239, 1945.
38. Dantzig, L., and Marshall, L. E.: Tropical lichen planus—New Guinea variety. New York State M. J., 1:991-995, 1946.
39. Davis, David B., and Bick, John W.: Skin reactions observed under wartime stress. J. Nerv. & Ment. Dis., 103:503-508, 1945.
40. Dobes, W. L.; Jones, J., and Franks, A. B.: J. Clin. Endocrinol., 5:412, 1945.
41. Drueck, C. J.: Pyogenic infections of the perineum and buttock skin. Am. J. Digest. Dis., 12:316, 1945.
42. Duckworth, G.: Meadow grass dermatitis. Brit. J. Dermat., 58:32, 1946.
43. Dunn, I. E.; Mason, H. S., and Smith, Barbara S.: A new technique for performing quantitative contact (patch) skin tests. J. Invest. Dermat., 6:323-336, 1946.
44. Epstein, A. A.: On the relation of the thyroid to allergic states. J. Mt. Sinai Hosp., 12:191, 1945.
45. Epstein, E.: Theophylline ethlenediamine as an antipruritic agent. Arch. Dermat. & Syph., 53:281, 1946.
46. Epstein, Stephan: Allergic skin diseases. Ann. Allergy, 3:301-323, 1945.
47. Epstein, Stephan: Treatment of allergic conditions with pyribenzamine and benadryl. Wisconsin M. J., 45:489-496, 1946.
48. Epstein, Stephan: Eczema—allergic dermatitis. Ann. Allergy, 2:247, 1944.
49. Epstein, Stephan: Is penicillin a photosensitizing agent? Arch. Dermat. & Syph., 54:70, 1946.
50. Epstein, Stephan, and Pinkus, Hermann: Penicillin dermatitis based on tuberculin-type sensitivity. Ann. Allergy, 4:186, 1946.
51. Eyerman, C. H.: Clinical experiences with a new antihistaminic drug. J. Allergy, 17:210-215, 1946.
52. Feinberg, M.: Allergy to penicillin (Editorial). J. Allergy, 16:302-304, 1945.
53. Feinberg, S. M., and Friedlaender, S.: J. Allergy, 16:296-298, 1946.
54. Feinberg, S. M., and Watrous, R. M.: Atopy to simple chemical compounds —Sulfonechloramides. J. Allergy, 16:209-220, 1945.
55. Felsher, Zachary, and Rothman, Stephen: The insensible perspiration of the skin in hyperkeratotic conditions. J. Invest. Dermat., 6:271-277, 1945.
56. Ferrer, Zanchi, and Bonduel: Abstract in J.A.M.A., 131:364, 1946.
57. Forman, J.: Int. Corr. Club of Allergy, 9:63-66, 1946.
58. Franks, A. G.; Dobes, Wm. L., and Romano, Dominic: Penicillin in the treatment of cutaneous disease. Arch. Dermat. & Syph., 52:14-16, 1945.
59. Franks, A. G.; Dobes, Wm. L., and Jones, J.: Tyrothricin in the treatment of diseases of the skin. Arch. Dermat. & Syph., 53:498-502, 1946.
60. Franks, Andrew G.: Contact dermatitis due to ace adherent. J. Allergy, 17: 112-113, 1946.
61. Friedlaender, S., and Feinberg, S. M.: Histamine antagonists. III. The effect of oral and local use of b-dimethylaminoethyl benzhydryl ether HCl on the whealing due to histamine. Antigen-antibody reactions, and other wheal-

ing mechanisms. Therapeutic results in allergic manifestations. J. Allergy, 17:129-141, 1946.
62. Gant, James I., Jr.: Dermatitis in the American Munitions Industry. Virginia M. Monthly, 72:158, 1945.
63. Garnier, G.: Relation of gonadal hormones to certain dermatoses. Nature, London, 156:339, 1945.
64. Gillespie, D. R., and Brown, P. W.: Blood dyscrasia with and without associated "atypical lichen planus." Minnesota Med., 29:575-577, 1946.
65. Ginsberg, J. E., and Shallenberger, P. L.: Wood's light fluorecscence phenomenon in quinacrine medication. J.A.M.A., 131:808-809, 1946.
66. Goldblatt, M. W.: Vesication and some vesicants. Brit. J. Indust. Med., 2:183-201, 1945.
67. Goldberg, Lawrence C.: An unusual lichenoid dermatosis. J.A.M.A., 130: 775-780, 1946.
68. Goldberg, L. C.: Penicillin in the treatment of cutaneous diseases. Arch. Dermat. & Syph., 52:184, 1945.
69. Goldman, L.: Cheilitis from local use of penicillin solution in mouth. Arch. Dermat. & Syph., 53:133, 1946.
70. Goldman, Leon; Friend, Forman, and Mason, Lester M.: Dermatitis from penicillin. J.A.M.A., 131: 883-890, 1946.
71. Goldsmith, W. N.: Ointment bases. Practitioner (London), 156:358-363, 1946.
72. Goodman, Herman: Eczema of the hands. Is it a diagnosis of ignorance? Urol. & Cutan. Rev., 50:62-66, 1946.
73. Goodman, H.: Rational pharmaceutical treatment of diseases of the skin. Clinics, 3:923-944, 1944.
74. Gordon, E. J.: Delayed serum sickness reaction to penicillin. J.A.M.A., 131: 727-730, 1946.
75. Gordon, H. H.: Treatment of ichthyosis. Arch. Dermat. & Syph., 57:178, 1945.
76. Gottschalk, H. R, and Weiss, R. S.: Epidermal sensitivity to penicillin. Arch. Dermat. & Syph., 53:365-371, 1946.
77. Gottschalk, Helen R.; Engman, M. F.; Moore, Morris, and Weiss, Richard S.: Penicillin ointment in the treatment of some infections of the skin. Arch. Derm. & Syph., 53:226, 1946.
78. Gougerot, H.: Avitaminose C cutanée. Ann. de dermat. et syph., 10:233-237, 1944.
79. Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Recurrent vesicular eruptions appearing during administration of penicillin. Arch. Dermat. & Syph., 50:6, 1944.
80. Guild, B. T.: Cutaneous detergents. Experience with an ether sulfonate compound. Arch. Dermat. & Syph., 51:6, 1945.
81. Hansen, Arild E.: Disturbances in lipid metabolisms in children. South. Med. J., 39:32, 1946.
82. Harris, M. Coleman: Contact dermatitis due to contact with chrome 17 per cent steel identification tags of the United States Navy. J. Allergy, 16:299-301, 1945.
83. Hartman, M. M.: Fleabite reactions, clinical observations and effect of histamine-azoprotein therapy. Ann. Allergy, 4:131-136, 1946.
84. Haswell, R. E., and Wilkinson, J. F.: Allergic reaction to parenteral penicillin. Lancet, 1:308, 1946.
85. Hatoff, Alexander: Desensitization to insect bites. J.A.M.A., 130:850-854, 1946.
86. Haxthausen, H.: Acta dermato-venereol., 24:286, 1943.
87. Haxthausen, H.: Allergic eczema caused by ethyl alcohol; elicited both by epicutaneous and internal application. Acta dermato-venereol., 25:527-528, 1945.
88. Haxthausen, H.: Pathogenesis of allergic eczema elucidated by transplantation. Experiments on identical twins. Acta dermato-venereol., 23:438-457, 1943.
89. Hellier, F. F., and Hodgson, G. A.: Penicillin in skin conditions. Lancet, 2: 462-464, 1945.
90. Henderson, Charles R., and Riley, Edward C.: Certain statistical considerations in patch testing. J. Invest. Dermat., 6:227-230, 1945.
91. Herrmann, F.: The inunction of allergens with "Intraderm." Ann. Allergy, 4: 4-12, 1946.
92. Hodgson, G. A.: Psychosomatic factors in some skin diseases. Brit. J. Dermat., 57:125, 1945.
93. Hughes, R. F., and McAllister, H. R.: Ann. Allergy, 3:207, 1945.
94. Hüllstrung, H.: Hautreaktionen nach Ungezieferstichen unter dem Bild eines Lichen urticatus. Arch. f. Dermat. u. Syph., 183:315-323, 1943.

95. Johnson, George D.: The use of histamine compound in the treatment of infantile eczema. J. South Carolina, 42:29-30, 1946.
96. Johnson, H. M.: Penicillin ointment in the treatment of infective diseases of the skin. Hawaii M. J., 5:185, 1946.
97. Jolliffe, Norman: Use of vitamins. J.A.M.A., 129:613-617, 1945.
98. Juon, M.: Le traitement peroral des dermatoses allergiques par le Pepto-Sulfene. Dermatologica, 92:158-160, 1946.
99. Kalz, F. G.: Psychological factors in skin disease. Canad. M. A. J., 53:247-253, 1945.
100. Kierland, R. R.: Local use of penicillin preparations in cutaneous diseases. Mil. Surg., 97:57, 1945.
101. Kierland, R. R.; Sheard, C.; Mason, H. L., and Lobitz, W. C.: Fluorescence of nails from quinacrine hydrochloride. J.A.M.A., 131:809-810, 1946.
102. Kilpinen, Olavi: Über einen Fall von durch Gummireizung hervorgerufenem Erythematodes. Acta dermato-venereol., 26:329-338, 1946.
103. Knudsen, Lila F.: A note on the statistical probabilities of finding hypersensitive subjects in random samples. J. Invest. Dermat., 6:231-232, 1945.
104. Kolodny, M. H., and Denhoff, E.: Reactions in penicillin therapy. J.A.M.A., 130:1058, 1946.
105. Lamb, J. H.: Allergic reactions during the administration of penicillin. Arch. Dermat. & Syph., 52:93, 1945.
106. Lamm, Stanley S.: Danger of injection of calcium gluconate in infancy. J.A.M.A., 129:347-348, 1945.
107. Lane, C. Guy: Occupational dermatoses: Disability and compensation. New England J. Med., 233:711-715, 1945.
108. Laycock, S. R.: Psychotherapy for the general practitioner. Canad. M. A. J., 53:230-235, 1945.
109. Leder, M.: Untersuchungen über die Hautwirkung von Glasfasern. Dermatologica, 91:138-147, 1945.
110. Levin, S. J.: Benadryl. Its use in allergic diseases. J. Allergy, 17:145-150, 1946.
111. Lomholt: Acta dermato-venereol., 26:314, 1946.
112. Lomholt, Sven: Extraordinary hypersensitiveness to cell wool. Acta dermat.-venereol., 26:282-285, 1946.
113. Longcope, W. L.; Luetscher, J. A.; Wintrobe, M. M., and Jager, V.: Treatment of arsenical poisoning with Bal. Bull. U. S. Army Med. Dep., 5:622, 1946.
114. Lutterloh, C. H., and Shallenberger, P. L.: Unusual pigmentation developing after prolonged suppressive therapy with quinacrine hydrochloride. Arch. Dermat. & Syph., 53:349-354, 1946.
115. Lynch, F. W.: Benadryl in dermatologic therapy. Arch. Dermat. & Syph., (in press).
116. Manson, R. C.: Penicillin in the treatment of pyogenic infections of the skin —a report of fifty cases. Virginia M. Monthly, 72:381, 1945.
117. Markson, L. S.: Dermatitis venenata following use of penicillin ointment. Arch. Dermat. & Syph., 52:384, 1945.
118. Mashkilleison, L. N.; Benyamovich, E. B.; Krichevskoya, E. D., and Shatamova, L. V.: The role of vitamins in the pathogenesis and treatment of skin diseases. Am. Rev. Soviet Med., 3:19-27, 1945.
119. Mason, H. S.: The allergenic principles of poison ivy; the synthesis of 3-n-pentadecyl-catechol. J. Am. Chem. Soc., 67:1538-1540, 1945.
120. Mayer, R. L.: Antihistaminic substances with special reference to pyribenzamine. J. Allergy, 17:153-165, 1946.
121. McGuire, J. A., and Shaffer, B.: Fixed bullous eruption due to sulfathiazole. Arch. Dermat. & Syph., 52:342-343, 1945.
122. Mellott, L. B., and Pfuetze, E. L.: Use of penicillin ointment in treatment of impetigo and other conditions of the skin. J. Kansas M. Soc., 47:7, 1946.
123. Mendelsohn, H. V.: Lemon grass oil. Arch. Dermat. & Syph., 53:94-98, 1946.
124. Michie, W., and Bailie, H. W.: A case of penicillin reaction. Brit. M. J., 1:554, 1945.
125. Montgomery, Royal M., and Casper, Esther A.: Cutaneous manifestations of the fungi causing dermatophytosis and Onychomycosis. J.A.M.A., 128:77-83, 1945.
126. Nickerson, W. J.; Irving, Laurence, and Nehmert, H. E.: Sandals, and hygiene and infections of the feet. Arch. Dermat. & Syph., 52:365-368, 1945.
127. Niedelman, M. V.: Occ. Med., 1:391, 1946.
128. Niedorff: Quoted from Strauss and Spain.[180]
129. Nisbet, T. W.: Arch. Dermat. & Syph., 52:221-225, 1945.

130. Nomland, R.: Cholinogenic urticaria and cholinogenic itching. Arch. Dermat. & Syph., 50:247-249, 1944.
131. Norrlind, Robert: Prurigo Besnier (Atopic dermatitis) Acta dermato-venereol., 26:1-168, 1946.
132. Notier, V. A., and Roth, G. M.: Treatment of hypersensitiveness to cold with benadryl. Report of a case. Proc. Staff Meet., Mayo Clinic., 21:170, 1946.
133. Obermayer, M. E. and Frost, K.: Arch. Dermat. & Syph., 51:309, 1945.
134. Obermayer, M. E.: A severe systemic reaction to a bee sting. Arch. Dermat. & Syph., 51:6, 1945.
135. O'Leary, P. A. and Farber, E. M.: Benadryl in the treatment of urticaria. Symposium on benadryl. Proc. Mayo Clinic, 20:417-445, 1945.
136. Olin, T. E.: Beitraege zur experimentellen Sensibilisierung der Haut mit 2-4-Dinitrochlorobenzol. Acta dermato-venereol., 25:135-162, 1945.
137. Osgood, Howard: Atopic sensitivity to caroid (Papain). J. Allergy, 16:245-250, 1945.
138. Palmer, Alice E.: Common disorders of the aging skin. Clinics, 4:1211-1229, 1946.
139. Park, R. G.: Allergy to egg-prepared vaccines. Brit. M. J., 2:570, 1945.
140. Peck, Samuel M., and Clare, H. C.: Dermatitis from dehydration of potatoes. Arch. Dermat. & Syph., 52:9-10, 1945.
141. Peck, S.: Discussion on Rostenberg and Kanof.[155]
142. Peck, S. M., and Rosenfeld, H.: J. Invest. Dermat., 1:237-265, 1938.
143. Pellerat, J., and Murat, M.: Ann. de dermat. et syph., No. 2:76-84, 1946.
144. Petersen, W. F.: Drug sensitivity on a non-specific basis. Ann. Alergy, 4:43-55, 1946.
145. Polano, M. K.: Marginalia zur dermatologischen Rezeptur. Dermatologica, 91: 297-309, 1945.
146. Pratt, A. G., and Corson, E. F.: Spread of dermatitis venenata by vesicle contents. Arch. Dermat. & Syph., 51:5, 1945.
147. Preston, J. F.,and Watkins, C. A.: Urticaria due to trinitrotoluene. Arch. Dermat. & Syph., 53:134-136, 1946.
148. Price, I. C.: Severe allergic reaction to intramuscular penicillin. Canad. M. A. J., 53:485, 1945.
149. Reingold, Irving M., and Webb, Frank: Sudden death following intravenous injection of thiamine hydrochloride. J.A.M.A., 130:491-492, 1946.
150. Report of the A.M.A. Council on Pharmacy and Chemistry: Dangers from the external use of sulfonamides. J.A.M.A., 128:1024-1025, 1945.
151. Robitzek, E. H.: Fatal pemphigoid reaction to diasone. Am. Rev. Tuberc., 51: 473, 1945.
152. Rokstad, Ingvald: Skin reactions caused by fractions of oil of turpentine and hexanitrodiphenylamine. Acta dermato-venereol., 26: supplementum 15:1-352, 1946.
153. Ronchese, F.: Generalized dermatitis from pediculosis capitis. New England J. Med., 234:665-666, 1946.
154. Rony, H. R., and Zakon, S. J.: Effect of endocrine substances on the human scalp. Arch. Dermat. & Syph., 52:323-327, 1945.
155. Rostenberg, Adolph, Jr., and Kanof, Naomi M.: Studies on eczematous sensitization. J. Invest. Dermat., 6:201-215, 1945.
155-(b). Rostenberg, A., Jr., and Welch, H.: A study of the types of hypersensitivity induced by penicillin. Am. J. M. Sc., 210:158, 1945.
156 Rothman, S.: Orland, F. J., and Flesch, P.: Group specificity of epidermal allergy to procaine in man. Invest. Dermat., 6:191-199, 1945.
157. Rowe, A. H.: Dermatitis of the hands due to atopic allergy to pollen. Arch. Dermat. & Syph., 53:437-453, 1946.
158. Rubin, S. S.: An allergic reaction following typhus-fever vaccine and yellow-fever vaccine due to egg yolk sensitivity. J. Allergy, 17:21-23, 1946.
159. Rudolph, J. A.: Contact dermatitis. Ann. Allergy, 4:79-114, 1946.
160. Satulsky, E. M.: Dermatitis venenata of the eyes and eyelids from the local use of penicillin. J. M. Soc. New Jersey, 43:95, 1946.
161. Schmitt, Ch. L.; Alpins, O., and Chambers, G.: Arch. Dermat. & Syph., 52: 226-238, 1945.
162. Schmidt, F. R.: Treatment of dermatoses with vasodilators. Arch. Dermat. & Syph., 52:344-346, 1945.
163. Schnitzer, A.: Klinische und experimentelle Erfahrungen mit dem Antihistaminmittel. Antergan. Dermatologica, 91:92-101, 1945.
164. Schnurman, A. G.: Five cases of latent trichophyton infection activated by the use of penicillin. Virginia M. Monthly, 73:281, 1946.

165. Schultz, A.: Ocular dermatitis from local penicillin; Report of two cases. Arch. Ophth., 35:145, 1946.
166. Schwartz, L.: Dermatitis from synthetic resins. J. Invest. Dermat., 6:239, 1945.
167. Schwartz, Louis, and Peck, S. M.: Dermatitis from wearing apparel. J.A.-M.A., 128:1209-1217, 1945.
168. Sezary, A.: (Occupational microbic eczema). Arch. d. mal. profess., 4:19, 1942.
169. Shaffer, L. W., Carrick, Lee, and Zackheim, H. S.: Use of benadryl for urticaria and related dermatoses. Arch. Dermat. & Syph., 52:243, 1945.
170. Shapiro, A. L., and Rothman, Stephan: Undecylenic acid in the treatment of dermatomycosis. Arch. Dermat. & Syph., 52:166-171, 1945.
171. Simon, Frank: Cutaneous reactions of persons with atopic eczema to human dander. Arch. Dermat. & Syph., 51:402-404, 1945.
172. Simon, F. A.: The pathogenesis of atopic eczema. South. M. J., 38:530, 1945.
173. Simon, F. A.: Personal communication.
174. Sizer, I. W., and Prokesch, C. E.: Inactivation of the irritant toxicants of poison ivy and related compounds by tyrosinase. Science, 101:517, 1945.
175. Smith, S. Watson: Eczema autolytica. Brit. M. J., 1:628-629, 1945.
176. Stannus, H. S.: Vitamin A and the skin. Brit J. Dermat., 5:201, 1945.
177. Stark, Vera: Percutaneous photosensitization due to handling parsnips. Acta dermato-venereol., 25:179, 1944.
178. State, D., and Wangensteen, O. H.: Procaine intravenously in treatment of delayed serum sickness. J.A.M.A., 130:990, 1946.
179. Stevens, F. A.: Status of poison ivy extracts. J.A.M.A., 127:912, 1945.
180. Strauss, Margaret B., and Spain, W. C.: Studies on poison ivy and other dermatitis-producing plants. J. Allergy, 17:1-10, 1946.
181. Strazza, John A.: Delayed sensitization to penicillin similar to serum sickness. J.A.M.A., 130:1071, 1946.
182 Strickland, D. A.: Penicillin sensitivity: Angioneurotic reaction. U. S. Navy M. Bull., 45:768, 1945.
183. Strickler, A., and Ginsburg, Th. M.: The sedimentation rate in the eczema of infants and children. Urol. & Cutan. Rev., 50:274-276, 1946.
184. Sugar, H. S., and Waddell, Wm. W.: Ochronosis-like pigmentation associated with the use of atabrine. J.A.M.A., 131:1460, 1946.
185 Sullens, W E.: Simulating serum-sickness reaction to penicillin. U. S. Nav. M. Bull., 45:752, 1945.
186. Sulzberger, M.: Discussion on Rostenberg and Kanof.[155]
187. Sulzberger, M. B., and Baer, R. L.: Yearbook of Dermatology and Syphilology. pp. 7-36. Chicago: Year Book Publishers, 1945.
188. Sulzberger, M. B., and Baer, R. L.: Yearbook of Dermatology and Syphilology. p. 155. Chicago: Year Book Publishers, 1945.
189. Sulzberger, M. B., and Baer, R. L.: Yearbook of Dermatology and Syphilology. p. 160. Chicago: Year Book Publishers, 1945.
190. Sulzberger, M. B., and Baer, R. L.: Studies in hypersensitivity to light. I. J. Invest. Dermat., 6:345-348, 1945.
191. Sulzberger, Marion B., and Emik, L. Otis: Studies on prickly heat. (1) Clinical and statistical findings. J. Invest. Dermat., 7:53-59, 1946.
192. Sulzberger, M. B.; Shaw, H. C., and Kanof, A.: Evaluation of measures for use against common fungous infections of skin. U. S. Nav. M. Bull., 45: 237-248, 1945.
193. Sulzberger, M. B., and Katz, J. H.: Absence of skin irritants. U. S. Nav. M. Bull., 41:1258-1262, 1943
194. Sulzberger, Marion B., and Zimmerman, H. M.: Studies on prickly heat. (2) Experimental and histologic findings. J. Invest. Dermat., 7:61-68, 1946.
195. Swineford, Oscar, Jr.: Anaphylactic shock from skin testing. J. Allergy, 17: 24-26, 1946.
196. Sylvest, Bent: Exanthema resembling lichen ruber during treatment with neosalvarsan. Acta dermato-venereol., 26:295-297, 1946.
197. Tate, B. C.: Urticaria and its treatment. Practitioner (London), 156:347-352, 1946.
198. Templeton, H. J.: Epidermal and dermal sensitization (coexisting in the same individual. J.A.M.A., 127:908-911, 1945.
199. Tobias, Norman: The use and abuse of sulfonamides in the treatment of skin diseases. Internat. M. Digest, 47:215-217, 1945.
200. Toland, J.A.L.: Letters Int. Corr. Club of Allergy, 9:122, 1946.
201. Török, L.: Dermatologica, 90:15-26, 1944.
202. Truitt, G. W.: Reactions to penicillin. Ann. Allergy, 4:196-198, 1946.

203. Turnbull, John A.: Some dermatologic aspects of allergy. Am. J. Digest. Dis., 13:9-14, 1946.

204. Urbach, Erich: Skin diseases due to vitamin deficiencies. Pennsylvania M. J., 49:833-839, 1946.

205. Urbach, E., and Gottlieb, P. M.: Skin Diseases, Nutrition, and Metabolism. New York: Grune & Stratton, 1946.

206. Underwood, G. B.; Gaul, L. E.; Collins, E., and Mosby, Mable: Overtreatment dermatitis of the feet. J.A.M.A., 130:249-256, 1946.

207. Vaisberg, M.: Combined tyrothricin-penicillin therapy in contact dermatitis. Ann. Allergy, 3:451, 1945.

208. Vickers, H. R.: Contact dermatitis caused by penicillin. Lancet, 1:307-308, 1946.

209. Waisman, M., and Gots, J. S.: Topical penicillin treatment of pyogenic infections of skin. Bull. U. S. Army Med. Dept., 4:516, 1945.

210 Waldbolt, G. L.: Clinical results with benadryl. J. Allergy, 17:142-144, 1946.

211. Walters, Joseph: A cutting punch biopsy forceps. Brit. J. Radiol., 19:203, 1946.

212. Watson, E. H.: Boric acid. J.A.M.A., 129:332-333, 1945.

213. Welch, H. and Rostenberg, A: J.A.M.A., 126:10, 1944.

214. White, Cleveland: Occupational dermatoses. Illinois M. J., 87:227, 1945.

215. Wiessema, M. U.: Über Salvarsanexantheme unter dem Bild von Ekzematiden. Arch. f. Dermat. u. Syph., 179:99-108, 1938.

216. Wilensky, A. O.: Fatal delayed anaphylactic shock after penicillin. J.A.M.A., 131:1384, 1946.

217. Wiseman, J. R.; and McCarthy-Brough, M. P.: Skin sensitivity in the aged —Fatality following intradermal tests. J. Allergy, 16:250-252, 1945.

218. Witherspoon, Frank G.: Exfoliative dermatitis associated with amebic dysentery. Arch. Dermat. & Syph., 53:506-507, 1946.

219. Yonkman, F. F.; Hays, H. W., and Rennick, Barbara: The protective action of N'-pyridyl-N'-benzyl-N-dimethylethylene-diamine HCl against horse serum anaphylaxis in dogs. Federation Proceedings, 4: 1945.

220. Zakon, S. J., and Kahn, J. B.: Urticaria from perfume. Arch. Dermat. & Syph., 52:11-13, 1945.

221. Zeller, M.: Penicillin urticaria. Ann. Allergy, 3:361, 1945.

Contact Testing of the Buccal Mucous Membrane

(Continued from Page 460)

3. Goldman, Leon: Cheilitis from local use of penicillin solutions in mouth. Arch. Dermat. & Syph., 53:133, (Feb.) 1946.

4. Goldman, Leon, Friend, Forman, and Mason, Lester M.: Dermatitis from penicillin with special reference to the development of eczematous hypersensitivity. Report of thirteen cases of contact dermatitis. (In press.)

5. Goldman, Leon, and Goldman, Capt. Bernard: Contact testing of the buccal mucous membrane for stomatitis venenata. Arch. Dermat. & Syph., 50:79, (Aug.) 1944.

6. Urbaitis, John C.: Penicillin reaction. Queries and Minor Notes, J.A.M.A., B 1, (May 4) 1946. Also personal communications to the authors.

7. Wright, Roy B., and Rule, W., Jr.: Penicillin lozenges in the treatment of oral lesions. J. California State Dent. A. 177, (Dec. 21) 1945. Abstracted in Dentistry, 6:636, (June) 1946.

News Items

INTERNATIONAL ASSOCIATION OF ALLERGISTS

The International Association of Allergists is sponsoring the formation of an International Board for the Certification of Allergists. Following the establishment by the College of the American Board for the Certification of Allergists, there were numerous requests by oustanding allergists in other countries for recognition by certification as specialists in allergy. This indicated that full certification in allergy is in great demand in all countries. The same purposes, aims, and ideals among doctors will establish such high standards for certification that it will be recognized internationally in all countries. Such a step will serve to accelerate research, to consolidate all of our investigative efforts, and to set a high goal which will be an incentive to the young physicians to apply allergy properly to their practice.

It is interesting that over a year following the establishment of the International Association of Allergists, a World Medical Association has been established with aims and purposes which correspond closely to those of the International Association as set forth in its Constitution. The platform adopted by the new World Medical Association as quoted in the *J.A.M.A.*, 132:450, October 26, 1946, is, among other things, "to promote closer ties among the national medical associations and among the doctors of the world by personal contact and all other means available in order to assist all peoples of the world to attain the highest possible level of health; to study the professional problems which confront the profession; and to organize an exchange of information on matters of interest to the profession."

The national allergy societies of the following countries have officially become members of the International Association of Allergists: Sweden, Denmark, Switzerland, France, Australia, Colombia, Chile and Argentina; the representative allergists of Cuba and Brazil; and two national allergy societies of the United States, The American College of Allergists and The American Society of Ophthalmologic and Otolaryngologic Allergy. Negotiations for membership are now being made with Canada, England, Italy, Peru and Scandinavian countries other than those mentioned above.

Details concerning the International Board for the Certification of Allergists will be announced at the appropriate time.

COLLEGE REGIONAL SPRING CLINICAL COURSE IN ALLERGY

The Mississippi Valley Sectional Instructional Course in Allergy, as announced in the September-October issue of the ANNALS OF ALLERGY, will be held under the auspices of the University of Kansas School of Medicine, Kansas City, Kansas, for four days, May 5 through 8. The hours will be from 9:00 to 12:15 and from 2:00 to 5:45. This course is for the purpose of acquainting physicians with the fundamentals of diagnosis and treatment of allergic diseases. The heads of the Departments of Physiology, Bacteriology, Pharmacology, Internal Medicine, Dermatology, Pathology, and Roentgenology of the University will present lectures emphasizing the importance of the various specialties in relation to allergic diseases. There will be clinics and a round-table discussion at the end of the course. The faculty will be announced in the January-February issue of the ANNALS OF ALLERGY and various other medical journals. The fee for the course is $50.

For details, write to Dr. Orval R. Withers, Suite 1418, Bryant Building, Kansas City 6, Missouri.

NEWS ITEMS

THIRD ANNUAL SESSION AMERICAN COLLEGE OF ALLERGISTS

Important Notice to Those Attending or Wishing To Present Papers

The American College of Allergists will hold its next annual scientific session at the Hotel Senator in Atlantic City on June 6, 7, and 8, 1947. The first day, June 6, will be occupied with special meetings and a symposium on molds. The general sessions of the College on June 7 and 8 will be open to Fellows and Associates of the College for the presentation of papers.

In addition to papers of the usual length with presentation time up to twenty minutes, the Program Committee has decided to permit those desiring to present short papers to do so, with the special purpose of encouraging brief clinical reports and preliminary communications not ready for final publication.

In accordance with this new policy, physicians and those in the related clinical sciences are invited to send to the chairman of the Program Committee summaries of original work, whether experimental or clinical, not exceeding 250 words in length, the presentation of which shall not exceed eight minutes. There is no limit to the number of papers of this type which anyone may submit and be accepted for publication, but only one may be presented at the meeting if accepted by the Program Committee. Those unable to attend the meeting may also send in papers which will be published in the program "by title." Presentation "by title" will give the author priority, and the abstract of the paper will be published in the ANNALS OF ALLERGY, together with the abstracts of all the papers which have actually been presented at the meeting. Indeed, the author may choose to present the paper "by title" and not present the paper at the meeting himself even though he attends the meeting. Presentation of a paper "by title" does not preclude publication in full in the ANNALS OF ALLERGY when sufficient data has been accumulated.

The foregoing plan of supplementing the regular program of the College by presentation "by title" will increase the scope of the work to be viewed by the College, will offer the opportunity for discussion of early experimental data, and will increase the interest of physicians in creative work in allergy even though on a small scale.

Titles and abstracts with any questions regarding this new policy should be sent as soon as possible to the chairman of the Program Committee.

Those desiring to submit abstracts "by title" or to present longer papers should send them to Dr. Harold A. Abramson, chairman, Program Committee, 133 East 58th Street, New York *22*, New York.

SCHOLARSHIPS AWARDED FOR INSTRUCTIONAL COURSE

Ten scholarships of $100 each were awarded at the recent College Fall Instructional Course held under the auspices of the Jefferson Medical College, Philadelphia. These scholarships were made available through the generosity of Almay, Inc., New York, and Marcelle Cosmetics, Inc., Chicago. Each firm contributed $500 towards this worthy fund. We are very grateful to the donors for making this available. The Committee on Arrangements carefully selected the applicants to receive this honor, based upon information relative to the merits of each. Those who received scholarship were Dr. Elsie M. Morris, Dr. Gertrude Sobel, Dr. George A. Watson, Dr. Clifford Kalb, Dr. S. Mackoff, Dr. James T. Spencer, Dr. Henry H. Alderfer, Dr. Julio Cueva, Dr. James N. Yamazaki and Lt. John J. Piel.

FALL INSTRUCTIONAL COURSE

The recent Fall Instructional Course was held under the auspices of the Jefferson Medical College in Philadelphia. It was one of the most successful and largest attended courses of instruction in allergy.

Thirty-seven instructors participated. Space will not permit the republication of the names of the entire faculty, which have appeared in a previous issue of the ANNALS. There was an address of welcome by Dr. William Harvey Perkins, dean of the Jefferson Medical College, and a lecture on "Antibiotics in Allergy" by Dr. Hobart Reimann, professor of medicine of the Jefferson Medical College. On Thursday afternoon, November 7, there were very successful laboratory and clinical sessions. An interesting round-table discussion completed the course on Saturday afternoon, November 9.

There were 232 registrants for the course, including an enrollment of seventy-two veterans. The course was accepted by the Veterans Administration and this required the approval of the Pennsylvania Department of Public Instruction. It also received the recommendation of the Council on Medical Education and Hospitals of the American Medical Association.

The next Fall Instructional Course will be held in November, 1947, under the auspices of the University of Cincinnati.

QUARTERLY REVIEW OF ALLERGY AND APPLIED IMMUNOLOGY

The Washington Institute of Medicine, which publishes the nine *Quarterly Reviews* covering the various specialties in medicine, and of which Henry J. Klaunberg, Ph.D. is president, plans to publish a new journal, *The Quarterly Review of Allergy and Applied Immunology*. The first issue of this new *Quarterly Review* will appear on April 1, 1947.

The men who have been selected as members of the Editorial Board of the *Quarterly Review of Allergy and Applied Immunology* are the following:

F. W. Wittich, *Editor-in-Chief,* Minneapolis, Minnesota
Stephan Epstein, Marshfield, Wisconsin
French K. Hansel, St. Louis, Missouri
David Harley, London, England
Holger Haxthausen, Copenhagen, Denmark
Bayard T. Horton, Rochester, Minnesota
W. Jadassohn, Geneve, Switzerland
Paul Kallós, Helsingborg, Sweden
A. Oliveira Lima, Rio de Janeiro, Brazil
Guido Ruiz-Moreno, Buenos Aires, Argentina
G. Estrada de la Riva, Havana, Cuba
Morris Scherago, Lexington, Kentucky
Albert Stoesser, Minneapolis, Minnesota
J. Warrick Thomas, Richmond, Virginia
Erich Urbach, Philadelphia, Pennsylvania
Alfred J. Weil, Pearl River, New York

SOUTHEASTERN ALLERGY ASSOCIATION

The second annual session of the Southeastern Allergy Association will be held at the Atlanta-Biltmore Hotel, Atlanta, Georgia, on January 18 and 19, 1947.

Dr. Hal M. Davison, 207 Doctors Building, Atlanta, Georgia, is president, and Dr. J. Warrick Thomas, 201 West Franklin Street, Richmond, Virginia, is vice president of the Southeastern Allergy Association.

Dr. Katharine B. MacInnis, 1515 Bull Street, Columbia, South Carolina, the secretary-treasurer of the Association, writes that the program is not entirely finished, but that among the papers will be the following:

"Contact Dermatitis"—Leon Unger, Chicago.
"Medical Management of Bronchial Asthma"—W. C. Spain, New York City.
"Modern Allergic Ideas and Treatment"—Harry Rogers, Philadelphia.
"Treatment of the Acute Asthmatic Attack"—Mason Lowance, Atlanta.

"Gastrointestinal Allergy"—J. A. Rudolph, Miami Beach.
"The Significance of Skin Tests in Drug Sensitivity"—Oscar Hansen-Pruss, Durham.
"Urticaria and Angioneurotic Oedema"—Ben Miller, Columbia, S. C.
"X-ray Therapy as an Adjunct in the Treatment of Bronchial Asthma"—Katharine Baylis MacInnis, Columbia, S. C.
"Allergy in a Small Town"—T. Luke Glennan, Denmark, S. C.
"The Importance of Predisposing and Contributory Factors in an Allergic Evaluation"—Nelson Zivitz, Miami Beach.
"The Allergic Child"—Walker H. Rucks, Memphis.
"Perfume Sensitivity"—Dave Thomas, Augusta, Ga.
"Pulmonary Tuberculosis and Allergic Asthma"—Norman Van Wezel, Montgomery, Ala.

It is hoped that as many as possible of the members of the College will attend this session.

NATIONAL ALLERGY RESEARCH AND WELFARE FOUNDATION

At the meeting of the Board of Regents of the College, November 3, 1946, in Philadelphia, a ruling was made that there would be no official relationship between the American College of Allergists and the American Allergy Fund.

Pursuant to the aims and purposes of the College, as set forth in its charter and as set forth in an editorial in the ANNALS, the March-April, 1946 issue, the College has established the National Allergy Research and Welfare Foundation.

Members appointed to the committee for this Foundation are:

Leon Unger, M. D., *Chairman*
Harold Abramson, M.D.
Ethan Allan Brown, M.D.
Hal M. Davison, M.D.
Jerome Glaser, M.D.
M. Murray Peshkin, M.D.

SOUTHWEST ALLERGY FORUM—MEETING AND ROSTER

Dr. Sim Hulsey, 505 Medical Arts Building, Fort Worth, Texas, secretary-treasurer of the Southwest Allergy Forum, announces that the next meeting will be held in the Washington-Ouree Hotel, March 31 and April 1, 1947, at Shreveport, Louisiana. It is hoped that the program for this meeting will be announced in the January-February issue of the ANNALS. Dr. J. S. Shavin, 803 Jordon Street, Shreveport, a member of the Executive Committee, desires that hotel reservations be made with him now.

The membership roster of the Southwest Allergy Forum as of April, 1946, is as follows:

Axelrod, Dr. A., Houston, Texas
Barnes, Dr. Maurice, Waco, Texas
Beard, Dr. O. W., Galveston, Texas
Berger, Dr. J. P., Wichita, Kans.
Black, Dr. J. H., Dallas, Texas
Blum, Dr. S. L., Beaumont, Texas
Blue, Dr. Johnny A., Oklahoma City, Okla.
Boggs, Dr. Whitney, Shreveport, La.
Bowen, Dr. Ralph, Houston, Texas
Braden, Dr. A. H., Houston, Texas
Brodkey, Dr. M. H., Omaha, Nebr.
Browning, Dr. Wm. H., Shreveport, La.
Burbidge, Dr. E. L., Detroit, Mich.
Burnett, Dr. J. R., Bartlett, Texas
Buscher, Dr. C. S., Champaign, Ill.
Cazort, Dr. Alan, Little Rock, Ark.
Cohen, Dr. Stanley, New Orleans, La.
Cope, Dr. E. P., Little Rock, Ark.
Denny, Dr. Rankin, Tulsa, Okla.
Derbes, Dr. V. J., New Orleans, La.
Dutton, Dr. L. O., El Paso, Texas
Edrington, Dr. N. K., New Orleans, La.
Efron, Dr. Bernard G., New Orleans, La.
Egbert, Dr. O. E., El Paso, Texas
Emery, Dr. O. J., Fort Worth, Texas
Engelhardt, Dr. H. T., Houston, Texas
Faber, Dr. E. G., Tyler, Texas
Fleming, Dr. Paul D., Houston, Texas
Glover, Dr. C. H., Memphis, Tenn.
Gordon, Dr. Samuel H., Ph.D., Richmond Hill, N. Y.
Grossman, Dr. Saul, Corpus Christi, Texas
Grow, Dr. Max, Dallas, Texas
Halpin, Dr. L. J., Cedar Rapids, Iowa
Harris, Dr. J. Harley, Memphis, Tenn.
Harris, Dr. J. Wade, Houston, Texas
Harris, Dr. Robin, Jackson, Miss.
Hawkins, Dr. Beatrice, Brownsville, Texas
Hawkins, Dr. W. W.,
Henry, Dr. John P., Memphis, Tenn.
Herring, Dr. P. S., Vicksburg, Miss.
Hightower, Dr. L. D., Fort Worth, Texas

(Continued on Page 510)

BOOK REVIEWS

ALLERGY. Second edition. Erich Urbach, M.D., and Philip M. Gottlieb, M.D. 968 pages, 412 figures. Price $12.00. New York, New York: Grune and Stratton, 1946.

The first edition, which was reviewed in the July-August, 1943, issue of the ANNALS, was translated into Portugese and Spanish; and the second edition is being translated into French and German.

There is a wealth of new material in the second edition, which appears only three years later than the first, showing the rapid progress in the field of allergy. Several complete sections have been added, all have been revised, and a number considerably enlarged. The following complete sections were added: Rh factor, allergic bronchitis, allergic cough, eosinophilic erythedema, and psychosomatic aspects of allergy. Up-to-the-minute information is to be found in the enlarged sections on drug allergy, with particular attention to sulfonamides, penicillin, and thiouracil; on endogenous allergy, toxic and allergic contact dermatitis, treatment of migraine, sensitivity to human plasma, pathogenesis of lupus erythematosus, periarteritis nodosa, and rheumatic fever; on methods of testing, diagnosis and complications of asthma, demonstration of cellular antibodies in allergic dermatitis, and the complete list of concentrations used in patch testing. All obsolete material has been eliminated.

The book is divided into three parts with thirty-five chapters. Part one deals with the fundamentals of allergy and our modern concept of them. Part two deals with etiologic agents of allergic diseases, and part three, the symptomatology and therapy of allergic diseases. The appendix contains copies of clinical records, physical examinations, histories pertaining to the various phases of allergy, et cetera. The book is well balanced; but the author, being an international authority on dermatologic allergy, presents an exhaustive treatise of this subject.

It was necessary to make 1,300 additional references to the literature of the last three years. Unquestionably it makes this volume the most complete standard work on allergy today. It is exceptionally well organized and is encyclopedic in scope. At the same time the authors have succeeded very well in making it eminently practical when presenting all phases of allergy.

The entire book has been reset in two-column format, which reduces the bulk of the volume without sacrificing necessary information. The illustrations are excellent and representative.

Although comprehensive and scholarly, it is presented in such a practical manner that it becomes an indispensable book for the general practitioner as well as the specialist.

F. W. W.

IT'S AN ALLERGY! By Frank G. Crandall, Jr., M.D. 313 pages, not including index. Illustrated. Price $3.50. Hollywood, California: Murray & Gee, Inc., 1946. This is an authoritative book written for the layman and the allergic patient.

There are many interesting case histories illustrating the usual symptoms of the common allergic manifestations, such as asthma and hay fever, as well as common allergic ailments. One is impressed with the scope of its information for the allergic patient. It apparently contains much new information which does not appear in other books of this nature. Even allergists will find material which they can use every day, and it can readily be used as a handbook on the desk at all times. The allergist can safely recommend this book for his patients.

It is dignified and clearly presented, and describes fully definitions and the frequency, diagnosis, and treatment of allergic states. Any victim of allergy should

have a much clearer understanding of the probable cause of his allergies and the patients in a very simple readable language should be valuable, both to the patient and the physician, when helping to regulate the patient's living in an effort to obtain the greatest relief and in receiving intelligent co-operation. Technical terms are explained whenever used.

There are chapters dealing with the frequency, diagnosis, and treatment of allergy, as well as special chapters on cosmetic allergy, hay fever and allergic rhinitis; asthma; skin allergy; gastro-intestinal allergy; migraine and other allergic headaches; allergy of the nervous system; eye, ear, nose, and throat allergy; physical allergy; miscellaneous allergies; and advice to the allergic patient. The common offenders of the ingestants, contactants, and inhalants are listed. The final chapter of advice to allergic patients is most complete. Throughout the book there is a very optimistic attitude.

It may have been difficult to present the subject of intrinsic allergy. However, patients should know something about the immunologic type of asthma as a result of hypersensitivity to antigens of infectious agents.

On the whole, however, the book is very complete when presenting to the patient extrinsic allergies.

Southwest Allergy Forum

(Continued from Page 508)

Hoben, Mr. R. E., Little Rock, Ark.
Holland, Dr. Lang F., Austin, Texas
Horton, Dr. Bayard T., Rochester, Minn.
Hosen, Dr. H., Port Arthur, Texas
Hotchkiss, Dr. DeWitt, Houston, Texas
Howell, Dr. J. B., Dallas, Texas
Huber, Dr. Harry L., Chicago, Ill.
Hulsey, Dr. Sim, Fort Worth, Texas
Jackson, Dr. Martha Beal, San Antonio, Texas
Jones, Dr. Edley N., Vicksburg, Miss.
Kahn, David, Camp Van Dorn, Miss.
Kahn, Dr. I. S., San Antonio, Texas
Kirchner, Dr. T. E., Albuquerque, N. M.
Koran, Dr. V. L., Detroit, Mich.
Leney, Dr. Fannie Lou, Oklahoma City, Okla.
Leopold, Dr. Howard C., Memphis, Tenn.
Lewis, Dr. B. O., Boston, Mass.
Lowance, Dr. M. I., Atlanta, Ga.
McComiskey, Dr. A. J., New Orleans, La.
McNeill, Dr. P. M., Oklahoma City, Okla.
Markland, Dr. James, Tulsa, Okla.
Marr, Dr. Wm. L., Galveston, Texas
Marsh, Dr. Carl D., Springfield, Ohio
Miller, Dr. N. L., Oklahoma City, Okla.
Montgomery, Dr. R. R., Long Beach, Calif.
Morrow, Dr. Marie B. (Honorary), Austin, Texas
Muller, Dr. J. E., Baltimore, Md.
Murphy, Dr. Faye B., Jackson, Miss.
Musick, Dr. E. R., Oklahoma City, Okla.
Nowicki, Dr. V. A., Camp Van Dorn, Miss.
Ogden, Dr. Henry D., New Orleans, La.
O'Byrne, Dr. George T., Corpus Christi, Texas
Owen, Dr. George W., Jackson, Miss.
Parson, Dr. George W., Texarkana, Texas
Parsons, Dr. E. J., Springfield, Ohio
Penfound, Dr. William T., New Orleans, La.
Petit, Dr. Paul T., Beaumont, Texas
Pilchner, Dr. John, Corpus Christi, Texas
Pounders, Dr. Carroll M., Oklahoma City, Okla.
Prince, Dr. Homer E., Houston, Texas
Randolph, Dr. Theron C., Chicago, Ill.
Reinarz, Dr. B. H., San Antonio, Texas
Rinkel, Dr. Herbert J., Kansas City, Mo.
Rouse, Dr. J. W. H., San Antonio, Texas
Rucks, Dr. W. L., Memphis, Tenn.
Rudolph, Capt. T., Augusta, Georgia
Rugeley, Dr. F. R., Wharton, Texas
Russell, Dr. Merle, Erie, Penn.
Sanders, Dr. J. P., Shreveport, La.
Schuey, Dr. Charles B., Dallas, Texas
Schwartzberg, Dr. Sam, San Antonio, Texas
Seibold, Dr. George J., Houston, Texas
Sellers, Dr. Erle D., Abilene, Texas
Service, Dr. W. C., Colorado Springs, Colo.
Shavin, Dr. J. S., Shreveport, La.
Shelmire, Dr. Bedford, Dallas, Texas
Shelton, Dr. Josephine, Refugio, Texas
Sheppard, Dr. Mary, Oklahoma City, Okla.
Shontz, Dr. D. D., Massillon, Ohio
Sievers, Dr. Ed F., St. Louis, Mo.
Silverthorn, Dr. L. E., Oklahoma City, Okla.
Steen, Dr. W. B., Tucson, Arizona
Swinny, Dr. Boen, San Antonio, Texas
Terrell, Dr. Truman C., Fort Worth, Texas
Thiberge, Dr. N. F., New Orleans, La.
Well, Dr. Clarence K., Montgomery, Ala.
Whigham, Dr. H. E., McAllen, Texas
Withers, Dr. Orval, Kansas City, Mo.
Wittich, Dr. Fred W., Minneapolis, Minn.
Wolf, Dr. A. Ford, Temple, Texas
Womack, Dr. N. C., Jackson, Miss.
Youman, Dr. J. D., Jr., Shreveport, La.
Zink, Dr. Pearl, San Antonio, Texas

Index to Volume 4

A

B

INDEX TO VOLUME 4

C

D

E

F

G

H

I

J

K

L

ANNALS of ALLERGY

PUBLISHED BY THE AMERICAN COLLEGE OF ALLERGISTS

American College of Allergists
Third Annual Session
Atlantic City - June 6-8, 1947

American Medical Association
Atlantic City - June 9-13, 1947

November-December
1946

Volume 4, Number 6 Published Bimonthly

ANNUAL SUBSCRIPTION $6.00 SINGLE COPIES $1.50

P

Q

R

S

T

U

V

W

THOMAS L. LUZIER
President and Founder of Luzier's Inc.

The Allergic Factor

Not infrequently, cosmetics figure as the offending factor or as a contributing factor in cases of allergy. When they do, there are two courses open to the patient: she can discontinue using cosmetics entirely or, with your help, she can find cosmetics which do not contain ingredients or combinations of ingredients that are offending to her. Obviously, the second course is preferable, when possible, because the average woman would be lost without certain cosmetic aids to good grooming.

Certain cosmetic ingredients, notably orris root and rice starch, are more highly allergenic than others. It is a good practice for a cosmetic manufacturer not to use such ingredients because there is a relatively high incidence of hypersensitivity to them. Other ingredients, however, which seldom figure as allergens or irritants may nevertheless prove to be the allergic factor.

That is why we believe that when there is a history or suspicion of allergy, the subject should be tested with the cosmetic preparations she is using or contemplates using. If tests with the finished products are positive, further testing with their constituents is indicated to endeavor to determine the offending agents. These found, it is frequently possible for us to modify our formulas to exclude them.

Luzier's Fine Cosmetics are selected to suit the individual's cosmetic requirements and preferences from a standpoint of whether her skin, viewed cosmetically, is normal, dry, or oily, and with regard to her coloring. We have a selection card for each of our patrons which roughly corresponds to a case history. Each of our selected products bears a label on which the patron's name and the registration number of the product are typed. Modified products bear a modification label. and a special modification card which carries a record of the patron's requirements is kept on file. We shall be pleased to send you our formulary, and in specific cases the raw materials for testing. We believe the patch test is best because it most closely approaches the conditions under which cosmetics are used.

Luzier's, Inc., Makers of Fine Cosmetics & Perfumes

KANSAS CITY, MO.

MEAD PRODUCTS
of Interest to Allergists

Nutramigen *1 lb. packages*	A feeding for milk-sensitive infants, which contains a non-antigenic form of nitrogen (Amigen) as the protein component, combined with other food essentials.
Sobee *1 and 4 lb. packages*	A soybean food designed as a substitute for infants exhibiting idiosyncrasy to milk protein.
Pablum *½ lb. and 1 lb.-2 oz. packages*	A palatable mixed cereal food, precooked and dried (needs no further cooking). Furnishes not only high food energy value but also thiamine and riboflavin and calcium, phosphorus and iron.
Pabena *8 oz. packages*	A new form of Pablum, in which the only cereal grain is oatmeal. Has essentially the same nutritional advantages of Pablum, and all of its convenient and economical points.
Mead's Dextri-Maltose with Yeast Extract and Iron *1 and 5 lb. tins*	Supplies, in addition to the carbohydrate value of Dextri-Maltose, thiamine and riboflavin (vitamins B_1 and G), and iron.
Mead's Oleum Percomorphum with Other Fish Liver Oils and Viosterol *10 and 50 c.c. bottles* *Bottles of 50 and 250 83-mg. capsules*	A source of vitamins A and D in which not more than 50% of the vitamin D content is derived from viosterol. Consists of liver oils of percomorph fishes, viosterol, and fish liver oil. Each gram contains not less than 60,000 vitamin A units and 8,500 vitamin D units (U.S.P.).
Mead's Cod Liver Oil Fortified with Percomorph Liver Oil *3 oz. and 16 oz. bottles*	Consists of Mead's Standardized Cod Liver Oil with percomorph and other fish liver oils. Not less than 50% of the vitamin content is derived from percomorph liver oil. Supplies not less than 6,000 vitamin A units and 850 vitamin D units (U.S.P.) per gram.
Mead's Standardized Cod Liver Oil *4 oz., 8 oz. and 16 oz. bottles*	Each gram supplies not less than 1,800 vitamin A units and 175 vitamin D units (U.S.P.).
Mead's Viosterol in Oil *10 c.c. and 50 c.c. bottles*	For disturbances of calcium-phosphorus metabolism. Supplies 10,000 U.S.P. vitamin D units per gram.
Mead's Cod Liver Oil with Viosterol *4 oz. and 16 oz. bottles*	Contains 1,800 vitamin A units and 400 vitamin D units (U.S.P.) per gram.
Mead's Viosterol in Halibut Liver Oil *10 c.c. and 50 c.c. bottles*	Supplies 60,000 vitamin A units and 10,000 vitamin D units (U.S.P.) per gram.
Mead's Halibut Liver Oil *10 c.c. and 50 c.c. bottles*	For vitamin A therapy. Each gram supplies 60,000 vitamin A units and 850 vitamin D units (U.S.P.)
Mead's Brewers Yeast Tablets *Bottles of 250 and 1,000 tablets*	For deficiencies of vitamin B complex. Each tablet contains not less than 0.06 mg. thiamine, 0.02 mg. riboflavin and 0.15 mg. niacin.
Mead's Brewers Yeast Powder *6 oz. bottles*	The same product as Mead's Brewers Yeast Tablets but supplied in powder form for use in infant feeding formulas.
Mead's Ascorbic Acid Tablets *Bottles of 50 and 250 tablets* *25 mg. and 100 mg. tablets*	For prevention and treatment of scurvy. Each tablet supplies 25 mg. of ascorbic acid, the equivalent of 500 International units of vitamin C. Also supplied in 100 mg. tablets.
Mead's Thiamine Hydrochloride Tablets *Bottles of 50 and 250 tablets* *1 mg. and 5 mg. tablets*	The anti-neuritic factor for prevention and treatment of beriberi and other deficiencies of vitamin B_1. Tablets containing 1 mg. thiamine supply 330 International units; 5 mg. tablets supply 1,650 International Units of vitamin B_1.
Mead's Riboflavin Tablets *Bottles of 50 tablets* *1 mg. and 5 mg. tablets*	Each tablet supplies 1 mg. of riboflavin (vitamin G). Also supplied in 5 mg. tablets.
Mead's Niacin Tablets *Bottles of 50 tablets*	For treatment of pellagra. Each tablet contains 25 mg. niacin.

MEAD JOHNSON & CO., Evansville, Indiana, U. S. A.